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SOME PHASES OF THE PATHOLOGY OF NUTRITION IN INFANCY*

W. McKIM MARRIOTT, M.D.

ST. LOUIS

Since the chief function of the infant is growth, it is not surprising that the nutrition of the infant should be the chief concern of those responsible for his welfare. Congenital anomalies of structure, acute and chronic infections, unsuitable food, unhygienic surroundings, too much attention or too little attention, in fact, almost any factor external or internal which can affect the infant at all has an influence on his nutrition. Scarcely any one portion or system of the body may become affected without involving the general nutrition. A growing realization that it is the infant as an organic whole that must be considered, rather than any individual organ, has led to a much broader conception of diseases in infancy and to more rational therapy. This is especially true of those diseases which are associated with gastro-intestinal disturbances. The time has passed when we center our attention exclusively on the alimentary tract and allow the infant to die of a curable derangement of the intermediary metabolism. The nutrition of the infant now claims our chief attention. The gastro-intestinal tract concerns us for the reason that any alteration in its function exerts a profound influence on the general nutrition.

The great importance of gastro-intestinal diseases as a factor in infant mortality is well recognized. We know that some infants suffering from diarrhea develop symptoms suggestive of acute poisoning and succumb within a relatively short time, while others lapse into a chronic state of malnutrition which only too often eventuates in death. We also know that exactly the same symptoms may occur in the case of infants who have not suffered from diarrhea. Czerny recognized this fact and grouped the causes of nutritional disturbances under three main heads: food, infection, and constitution. Granting the importance of these etiologic factors, we are still largely in the dark

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* Read before the Harvey Society, New York, March 27, 1920.

as to how each of them acts, as to what causes the symptoms and even as to why such infants suffering from nutritional disturbances should die. Very little information is obtained from the necropsy room. In the great majority of instances the pathologic findings on infants dead of nutritional disturbances are essentially negative.

In the absence of anatomic changes we are forced to conclude that some profound alteration in the chemical or physiologic processes in the body must have occurred. This conception has led to much investigation and more speculation as to the nature of these changes, and a popular idea has been that most of the symptoms are referable to toxic substances of metabolic or bacterial origin. Finkelstein [1] and his colleague, Meyer,[2] have especially emphasized the conception of "food poisoning" as a cause of nutritional disturbances. They consider infection and constitutional abnormalities chiefly as contributory factors in that they lower the infant's tolerance for food, that is, the ability to utilize food without the production of harmful substances. The fact that many of the symptoms are increased when excessive food is given has been the basis for this belief. An entirely different interpretation of this fact, may be made as will be seen later. Finkelstein and his assistants have made numerous attempts to determine the nature of the hypothetic poisons elaborated from food during the processes of metabolism but the experimental evidence has not been conclusive. Substances capable of producing all of the symptoms have not been found and no satisfactory explanation has been offered as to the exact mode of action of these hypothetical poisons or of the nature of the peculiar "tolerance" which permits some infants more than others to take large amounts of food without disturbance of the nutrition.

In the absence of proof of a "food poisoning" as the cause of symptoms, it would seem worth while to search for other possible explanations of the observed facts. It is the purpose of the present paper to present a brief account of such a search.

Two types of nutritional disturbances will be considered, one an acute toxiclike condition usually following severe diarrhea; the other, a chronic state of failing nutrition commonly known as "marasmus." The prominent symptoms of each condition will be mentioned and the cause of these symptoms discussed.

Striking symptoms are usually more easily explained than are less marked ones so the search for underlying causes began with a consideration of the most stormy of the nutritional disturbances. The

1. Finkelstein: Jahrb. f. Kinderh. **65**:1, 263, 1907; ibid. **68**:521, 693, 1908. Finkelstein and Meyer: Ibid. **71**:525, 1910.
2. Meyer: Jahrb. f. Kinderh. **65**:585, 1907.

condition referred to is known by various names such as "gastro-intestinal intoxication," alimentary intoxication," or "toxicosis." The symptoms are for the most part hyperacute but occur much more frequently in infants who have for some time been in poor nutritional condition, especially those who have suffered from previous attacks of diarrhea. Such an infant may develop diarrhea of more than usual severity. The stools increase in number and lose their normal character, becoming finally little more than brownish water passed in considerable volume, at times almost continuously. The much used term "cholera infantum" is fairly descriptive of the condition. Vomiting is frequently observed.

Coincident with the development of the diarrhea, there is a rapid loss of weight which, even in a small infant, may amount to as much as a half pound or a pound in a single day. The whole appearance of the patient changes. The features become sharpened, the eyes sunken and fixed in a far-away stare or turned upward under the half closed lids. The skin, especially over the forehead, is likely to assume a slate gray color. Over the body it hangs in loose folds; it is dry and has lost its elasticity so that it may be picked up into ridges which remain an appreciable interval before flattening out. The lips are dry, parched and often of a peculiar cherry red color. The mouth is held partly open, the tongue is dry. These infants are at first irritable and restless. There is a short, shrill cry, frequently repeated. Later the psyche becomes clouded and the infant lapses into a state of coma. Convulsions not infrequently close the scene. The respirations are deeper than normal, often of the "air hunger" type such as is observed in diabetic or uremic coma. The pulse is small, sometimes almost imperceptible, often rapid and irregular. The hands and feet are cold, although the rectal temperature is almost invariably elevated. The urine is very scanty, highly concentrated and may contain traces of albumin and a substance capable of reducing Fehling's solution. The blood is obtained with difficulty. It is thick, does not flow easily and when centrifuged separates a relatively small amount of serum. Some degree of leukocytosis is often present. There is in all marked cases a negative nitrogen and salt balance.

This clinical picture is a familiar one; it is described in some detail in order to indicate the nature and scope of the problem of determining the cause of each of the symptoms. The investigations here presented are by no means the first directed towards the solution of the problem. Various explanations for individual symptoms have been offered but in such a condition as this when a large number of symptoms are regularly and coincidentally present one must suspect

some underlying cause which provides an adequate explanation for *all* of the symptoms. Obviously the problem would have to be attacked first by a consideration of the individual symptoms.

The particular symptom which has probably received the greatest attention has been the peculiar "air hunger." Czerny [3] first drew attention to this and noted the resemblance of the breathing to that of acid poisoned animals. He suggested that abnormal acids had entered the circulation. Keller was unable to find such acids in the urine. Steinitz [4] suggested a loss of base from the body in the diarrheal stools as a cause of the acidosis but the observations of Holt, Courtney and Fales [5] and of Shohl [6] have failed to substantiate this hypothesis. Dr. Howland and I [7] demonstrated by various tests that acidosis was actually present, often of a severe grade and sufficient in itself to lead to death. We found that acidosis was not the result of over production of acetone bodies and suggested that it was in part due to a failure of the kidney to excrete acid phosphate. We were indeed successful in demonstrating an increase in the inorganic phospate content of the serum and were able to show that a similar phosphate retention occurred in the case of patients suffering from uremic acidosis.[8] We believed the failure of renal function to be a result of excessive water loss from the body by way of the bowel. Oscar Schloss [9] confirmed these findings and brought further evidence of impairment of renal function by demonstrating an excess of urea and total nonprotein nitrogen in the blood, reduced phenolsulphonephthalein excretion in the urine and an abnormally high Ambard coefficient. Schloss further demonstrated that the extent of renal function involvement was, in a general way, proportionate to the degree of desiccation of the blood.

That the blood of these infants is concentrated by water loss has been repeatedly shown by various observers (Reiss,[10] Salge [11] and Schloss [9]). There is an increase in the specific gravity, in the corpuscular volume, and in the amount of dried residue. The index of refraction is increased, and the protein content high. The viscosity, the electrical conductivity and the osmotic pressure are all increased.

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3. Czerny: Jahrb. f. Kinderh. **45**:271, 1897.
4. Steinitz: Jahrb. f. Kinderh. **57**:689, 1903.
5. Holt, Courtney and Fales: Am. J. Dis. Child. **9**:213 (Feb.) 1915.
6. Shohl: Unpublished work.
7. Howland and Marriott: Am. J. Dis. Child. **11**:309 (March) 1916.
8. Howland and Marriott: Arch. Int. Med. **18**:708 (Nov.) 1916.
9. Schloss: Am. J. Dis. Child. **15**:165 (Feb.) 1918.
10. Reiss: Jahrb. f. Kinderh. **70**:311, 1909; Ergeb. d. Inn. Med. u. Kinderh. **10**:531, 1913.
11. Salge: Ztschr. f. Kinderh., 1911, pp. 126, 317.

We know from the work of Starling [12] that with a colloidal osmotic pressure of the blood greater than the arterial pressure in the renal glomeruli, secretion of urine by the kidney ceases. This is the condition in these infants. They are virtually in a state of uremia as the result of a functional failure of the kidney.

The acidosis explains the air hunger breathing but not the other symptoms. It is in itself not usually the cause of death. It may be overcome by the administration of sodium bicarbonate by mouth or intravenously but in the great majority of cases symptoms other than those of acidosis are unchanged or may even be increased in severity and the infant succumbs. Treatment which may save the lives of patients suffering from other types of acidosis fails when applied to these infants. It is obvious, therefore, that other and more grave conditions than acidosis must be present and operative.

The clinical picture presented by these infants is in many respects not unlike that of surgical or wound shock. There is the same gray pallor, prostration, weak thready pulse and altered character of the respirations and very frequently rapidly fatal termination. The apparent similarity between the two conditions is so close that it has seemed worth while to attempt to determine whether or not some of the same factors were responsible in each.

This is not the place for a detailed discussion of wound shock; suffice it to say there is at one stage, a decrease in the amount of blood in currency, due to a passage of plasma through the vessel walls and also to the collection of blood at the periphery which is thus removed from effective circulation. This decrease in blood volume would lead to an immediate fall in blood pressure were it not for a compensatory constriction of the arterioles. In many instances this compensatory mechanism is inadequate and a considerable fall in blood pressure occurs. Diminished blood volume further results in a very greatly diminished volume flow of the blood. That is to say, a decreased amount of blood flows through a given portion of the body in a unit of time. Decreased volume flow of the blood leads to an accumulation of acid products of metabolism in the tissues and a decreased alkali reserve of the blood, that is to say, acidosis (Wright and Colebrook,[13] Gesell [14]).

The gray color of the skin, in shock, seems to be due to a stagnation of the corpuscular elements in the capillaries as a result of constriction of the arterioles. Cannon, Fraser and Hooper [15] have shown

12. Starling: J. Physiol. **24**:317, 1899.
13. Wright and Colebrook: Lancet **1**:763, 1918.
14. Gesell: Am. J. Physiol. **47**:472, 1919.
15. Cannon, Fraser and Hooper: J. A. M. A. **70**:526 (Feb. 23) 1918.

that red blood cell counts made on blood obtained from the capillaries by puncture of the skin are very appreciably higher than those made on blood taken directly from the veins.

Thus we see the symptoms of shock largely the result of a suddenly diminished blood volume. What of the infants with diarrhea who have many of the same symptoms? They too have a diminished blood volume. This, as has already been mentioned, is due to a drying out of the blood by excessive water loss.

In order to determine whether or not this decrease in the blood volume results in a diminished volume flow of the blood, we have applied the calorimetric method of G. N. Stewart.[16] The principle of this method is to immerse a portion of an extremity in a measured volume of water at a known temperature, somewhat below that of the body. The water is contained in a well insulated calorimeter. At the end of a ten minute period the temperature of the water in the vessel is measured. The increase in temperature, other factors being equal, is proportionate to the amount of blood passing through the extremity during the period of observation. The volume flow of the blood is conveniently expressed in terms of cubic centimeters per 100 gm. of body weight per minute. Dr. Kirsten Utheim[17] working in my laboratory has confirmed the accuracy of the method as applied to small animals by comparison with the results obtained by the use of the "Strohmuhr," measurements being made on the limbs and femoral arteries of dogs.

The Stewart method is easily adaptable to infants by using a vacuum food jar as a calorimeter. With proper control of the conditions we found that the volume flow of the blood in the arms or legs of infants could be determined with a very considerable degree of accuracy. It is, of course, essential that the infant should be quiet.

By the use of this calorimetric method, it was found that the volume flow of the blood in the arms of normal infants varied from 15 to 22 c.c. per 100 gm. per minute. Repeated determinations made on the same infant at different times of the day and on successive days gave remarkably constant results. In applying the method to infants suffering from the condition under consideration, a greatly diminished flow of the blood was found, this being in some instances as low as 2 or 3 c.c. per minute. In the greatly decreased volume flow of the blood of these infants we have another factor in the causation of acidosis, in addition to the failure of acid excretion, already alluded to. From what has been said regarding the nature of the acidosis in these cases, it becomes apparent why the administration of alkali alone usually fails to cure. Sodium bicarbonate,

16. Stewart: Heart **3**:33, 1911.
17. Utheim: Am. J. Dis. Child. **20**:366 (Nov.) 1920

administered in isotonic or hypertonic solution, does not increase the blood volume or volume flow and does not lower the osmotic concentration of the blood, so that secretion of urine may be resumed. Hypertonic solutions, in fact, have quite the opposite effect.

If the volume flow of the blood through the abdominal vessels is diminished to any such degree as it is in the extremities, one would expect that the functional ability of the gastro-intestinal tract to care for food would be greatly impaired. Such seems to be the case for it has been shown by Straub [18] that dogs rendered anhydremic by a diminished intake of water are very prone to the development of diarrhea and vomiting when fed. The same is certainly true of these infants.

Mention has been made of the presence of a reducing substance in the urine. L. F. Meyer [19] believed this sugar to be lactose or whatever disaccharid was contained in the diet. Finkelstein [20] has explained the appearance of these disaccharids in the urine as the result of a passage of undigested sugar into the circulation through the injured intestinal mucosa. Schloss,[9] on the other hand, found the sugar in the urine to be either glucose alone or glucose in combination with galactose or lactose. A certain amount of lactose can pass through the normal intestinal mucosa and it may well be the case that when fairly strong solutions of lactose are introduced into the intestinal tract of these infants that some would be absorbed unchanged. As lactose is not altered outside of the intestine, it would be excreted quantitatively in the urine. Even if occurring in the urine as claimed by Von Reuss and Meyer, the amount is too small to be considered as a factor of any importance in the production of symptoms. The glycosuria, however, requires explanation. It has been shown by Araki [21] that asphyxial conditions occurring as the result of vaso constriction, hemorrhage or a diminution of the oxygen carrying capacity of the blood, lead to glycosuria. This is generally supposed to be the result of increased glycogenolysis dependent upon acid production in the tissues. In the case of these infants the glycosuria may be readily explained on the same basis.

Diminished blood volume, such as occurs in the condition under discussion, is not necessarily accompanied by a lowering of blood pressure, such as is so frequently observed in shock. We have observed such a lowering only in exceptional instances. The high blood viscosity in these infants is likely a factor in maintaining blood pressure.

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18. Straub: Ztschr. f. Biol. **38**:537, 1899.
19. Meyer: Jahrb. f. Kinderh. **65**:585, 1907.
20. Finkelstein: Jahrb. f. Kinderh. **65**:263, 1907.
21. Araki: Ztschr. Physiol. Chem., Series of Articles in **15**: **16**: **17**: **19**.

It may be well to point out here that although a diminution in blood volume is common to the two conditions under consideration, the causes for the decreased blood volume are quite different. In the case of infants with diarrhea, there is a drying out of the blood by water loss; in shock, on the other hand, the diminished blood volume is the result of loss of plasma. The protein concentration of the serum in infants with diarrhea is high, in shock normal or low. In this difference, we have an explanation of the fact that in some instances the symptoms of the two conditions are identical, in others quite different.

That the same constriction of the arterioles occurs as a result of the diminished blood volume of these infants as has been observed in the case of shock patients, would be expected. A comparison of the red blood cell counts made on venous and on capillary bloods, showed a marked concentration of corpuscles in the capillaries. This stagnation of red blood cells in the capillaries as the result of arteriolar constriction, may well explain the peculiar gray pallor of the skin, which tends to disappear with establishment of a normal circulation.

From what has been said, it is apparent that the shocklike symptoms of these infants may reasonably be explained on the basis of the known blood volume decrease.

Constriction of the arterioles leads to a damming back of leukocytes in the capillary blood to even a greater extent than erythrocytes. For example, I have seen a difference of 5,000 in the leukocyte counts of venous and capillary bloods from the same infant. A moderate degree of leukocytosis, so often observed in patients of this type, may in part, be explained by this factor.

Fever, as has been mentioned, is commonly present in infants suffering from severe diarrhea. Suggested explanations have not been lacking. Finkelstein and his colleagues have considered the fever to be the result of pyrogenic substances in the circulation. The fact that feeding solutions of lactose or of sodium chlorid or injecting these substances intravenously, especially to infants already suffering from a nutritional disturbance, results in a rise in temperature has been interpreted as indicating that these substances may exert a direct influence on the nervous mechanism of the heat center or may so injure the cells of the body that abnormal metabolic processes are set up which result in the formation of toxic products capable of causing fever. Both salt and lactose when injected intravenously are quantitatively excreted unchanged. It is, therefore, necessary to assume that the effect observed must be of a physical chemical nature and not due to the chemical breakdown of the salt or lactose. These observations of Finkelstein on salt and sugar fever led to a great deal

of controversy. A very good summing up of the literature on this point is found in a recent article by Balcar, Sansum and Woodyatt.[22] Without going into further detail, it may be stated that the weight of evidence seems to strongly support the view that the action of sugar and salt is to remove water from the body and that the effects observed after the administration of sugar and salt are the result of removal of water from the body. Woodyatt and his collaborators, in the article just cited, bring forward excellent experimental evidence that fever may occur as the result of a decreased amount of water in the body available for evaporation. They have demonstrated that the fever resulting from the administration of solutions of sugar or salts is dependent not upon the total amount of these substances given but upon the amount of water simultaneously introduced into the body. Hypertonic solutions of unutilizable crystalloids leave the body, taking with them water. In the case of the injection of isotonic or hypotonic solutions or when water is administered simultaneously to supply the water deficit there is, according to these authors, no occurrence of fever.

The infants, of the type which we have been studying, are known to have a diminished water content and a high osmotic pressure of the blood, conditions which it has been shown are capable of leading to high temperatures. That these infants show a febrile reaction and that this reaction should be increased by the administration of hypertonic solutions of sugars or salts as was shown by Finkelstein is not surprising when we consider the fact that the dehydration is thus increased. There is no need for assuming injury to body cells or the production of pyrogenic metabolites.

Water evaporation is of even greater importance in heat regulation in the infant's body than in that of the adult. Thus Rubner and Huebner[23] have shown that as much as 55 gm. of water per kilo per day may be evaporated from the body of an infant as compared with a normal evaporation of 22 gm. per kilo per day in the adult. From 30 to 40 per cent. of the total loss of heat from the body is due to water evaporation. The mechanism of water evaporation may well be considered as a safety valve to prevent increase in body temperature. Rubner and Huebner found that when the metabolism of an animal was increased by feeding meat the evaporation of water increased 48.1 per cent., while the total caloric output was increased only 27.7 per cent. When the action of this safety valve is impaired by the increase of osmotic pressure of the body fluids, fever results very much in the same way as the overheating of a gasoline engine

22. Balcar, Sansum and Woodyatt: Arch. Int. Med. **24**:116 (July) 1919.
23. Rubner and Huebner: Ztschr. f. Biol. **38**:315, 1899.

when the radiator goes dry. Fever as the result of dehydration has been repeatedly observed in infants, in adults and in animals. Thus L. F. Meyer [24] saw it in the case of infants fed on a concentrated diet; Czerny [25] saw it in cats kept in a warm, dry atmosphere until the blood became desiccated; Jurgensen [26] observed temperatures up to 104 F. in adults undergoing Schroth's dry diet treatment.

The fever of the infants with the condition described can readily be explained on the basis of the dehydration which is known to be present. The picture is, however, often complicated by other factors. Infection cannot always be excluded. Indeed, in some instances, the presence of a parenteral infection may result in diarrhea and vomiting which leads to a dehydration of the body. Under such circumstances the fever may have a double explanation although Woodyatt suggests that even the fever of infection may be due to an insufficiency of free water in the body.

It has been mentioned that these infants during the stage of acute symptoms often excrete more nitrogen and salts than they take in. This negative nitrogen and salt balance can be interpreted only as the result of tissue destruction. That desiccation of the body results in such tissue destruction is well shown by the experiments of Straub [18] on dogs rendered anhydremic by an insufficient fluid intake. It is further of interest to note that Straub [27] has shown that the administration of salt to such animals results in a still greater negative nitrogen balance. This he interprets as the result of further dehydration brought about by the salt diuresis. Finkelstein has observed the same result following the administration of salt or lactose to infants, but has interpreted it as indicating a toxic action of sugar and salt, a conclusion with no proved basis of fact.

It has been mentioned that infants at about the time of the onset of the severe toxic symptoms suffer a loss in weight, greater than is seen in almost any other clinical condition. Losses of from one to two pounds even in the case of small infants and in a relatively short period of time are observed. This is greater than can be accounted for by anything but water loss. At the same time, examination of the blood shows a concentration which, if indicative of the desiccation of the other fluids of the body, could easily account for all of the loss of weight. The dry skin, lusterless eyes and sunken fontanel are clinical evidences of this water loss.

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24. Meyer, L. F.: Quoted from Langstein-Meyer Säuglingsernährung und Säuglingsstoffwechsel, Wiesbaden, 1914, p. 45.
25. Czerny: Arch. f. exper. Path. u. Pharm. **34**:268, 1894.
26. Jurgensen: Deutsch. Arch. f. Inn. Med. **1**:196, 1866.
27. Straub: Ztschr. f. Biol. **37**:527, 1899.

The conception presented gives us one explanation for the more frequent occurrence of the toxic states in warm weather. It has been shown [28] that an increase of external temperature from 20 to 36 C. may lead to a 600 per cent. increase in water elimination by the skin and lungs. In the case of infants with a lowered water reserve, such excessive loss by evaporation may easily lead to desiccation with its resulting symptoms. Rietschel [29] observed the development of toxic symptoms when weak infants were exposed to high room temperatures, and Finkelstein observed a lessening of intoxication symptoms when the infants were removed to cooler surroundings. In excessively hot weather infants, whether suffering from diarrhea or not, sometimes lapse into a state indistinguishable from that described as alimentary intoxication. The term "heat stroke" has been applied to this condition. There is little doubt that it is often the result of a desiccation of the body. The nervous symptoms presented by these infants are a combination of those observed in uremia and in shock. That the infants are virtually suffering from both of these conditions has already been shown.

To sum up: The entire clinical picture presented by infants who have lapsed into a toxic, shocklike condition following severe diarrhea may be explained on the basis of the water loss from the body, which is known to occur. That factors other than water loss are operative cannot be denied, but it is unnecessary to assume the existence of other factors in order to explain the observed facts. If poisons are accountable for the symptoms, their origin, nature and mode of action has not yet been explained. The supposed toxic action of sugar and salt have been discussed. Efforts to produce the symptoms in animals by feeding or injection of intestinal contents or extracts of intestinal contents of these infants have failed.[30]

Mellanby [31] has suggested B-imidazolethylamine (histamin), a product of bacterial action on histidin, as a cause of toxic symptoms. This substance when given by mouth to animals causes diarrhea and vomiting and when injected intravenously gives rise to shocklike symptoms, but the condition of the blood after such injection is quite different from that observed in these infants. There is no desiccation and the protein content is low or normal. The same may be said of the action of proteoses, which have been suspected of passing unchanged through the gastro-intestinal wall into the circulation.

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28. Langstein-Meyer: Säuglingsernährung und Säuglingsstoffwechsel, Wiesbaden, 1914, p. 41.
29. Rietschel: Monatschr. f. Kinderh. **9**:39, 1911.
30. Czerny and Salge: Quoted by Langstein-Meyer, Säuglingsernährung und Säuglingsstoffwechsel, Wiesbaden, 1914, p. 296.
31. Mellanby: Quart. J. Med. **9**:164, 1915.

So far no mention has been made of the original cause of the diarrhea. A full discussion of this question would occupy more time than that allotted to this paper. Suffice it to say that whether the diarrhea is the result of an excess of fat or carbohydrate in the food, whether it is secondary to parenteral infections or itself of infectious origin, whether due to nervous influences or the injudicious administration of cathartics, the end result is the same. Once anhydremia has occurred, a "vicious circle" is established which still further results in lowering the functional capacity of the gastro-intestinal tract. Heubner,[32] in voicing his skepticism concerning Finkelstein's conception of a food poisoning as the cause of the symptoms, draws attention to the fact that the clinical picture of Asiatic cholera, a disease entirely unrelated to food disturbances, is identical with that observed in infants supposedly suffering from food intoxication. He suggests that the younger generation of pediatricians are probably not familiar with Asiatic cholera and, therefore, take no cognizance of this fact in theorizing about the cause of the symptoms.

If a negative water balance occurring as the result of diarrhea leads to a characteristic symptomatology, the same symptoms should also occur as the result of a negative water balance dependent on other causes. This we have found to be the case. Dr. Perkins and I made a number of observations on infants who presented symptoms indistinguishable from those following severe diarrhea. As a criterion of the degree of desiccation of the body fluids we determined the index of refraction of the blood serum. This determination is one which is easily carried out within a few minutes time and requires only one or two drops of serum. It has the advantage that it may be repeated at frequent intervals. The refractive index varies with the concentration of solids in solution. As the protein has much greater effect on the index than the other solid constituents of the serum, it is possible, as shown by Reiss,[10] to determine quite accurately the protein content of the serum by means of the refractometer. By the use of this method he found the protein content of the serum of normal infants during the first six months of life to average about 6 per cent. Toward the end of the first year it was often as high as 7 per cent. These figures have been confirmed by Salge [11] and by ourselves. The protein content of the serum normally varies somewhat from day to day in the same infant, but the variations are not great. With a drying out of the blood the protein concentration necessarily increases. Such we have invariably found to be the case in the serums of infants suffering from the intoxicationlike symptoms following severe diarrhea. We have observed an increase

32. Heubner: Lehrb. d. Kinderh.

in the protein content of the serum of as great as 50 per cent. above the normal for the age. Applying the refractometric method, we were able to demonstrate a state of anhydremia in a number of conditions quite unrelated to diarrhea. For example, a microcephalic idiot 5 months old had taken only extremely small amounts of food or water for some days. This infant on admission to the hospital presented the typical symptoms of an intoxication with the sole exception of the diarrhea. The blood protein was 9.35 per cent. On the administration of a considerable amount of saline parenterally the protein content of the blood dropped to 6.6 per cent. At the same time, there was a disappearance of practically all of the symptoms of intoxication. This infant took very little of anything by mouth and two days later the blood protein had increased to 8.4 per cent. and toxic symptoms were again present. The administration of food by gavage resulted in vomiting and diarrhea, symptoms which had not been present previously. The child lost 400 gm. in weight during the succeeding twenty-four hours and the blood protein concentration rose to 9.5 per cent. The symptoms were those of an extreme degree of intoxication. Despite the parenteral administration of large amounts of saline, it was impossible to maintain a normal water content of the body. The protein concentration of the serum never again became lower than 8.2 per cent., and the symptoms remained present until death occurred. In this case the dehydration was originally brought about by an insufficient fluid intake. When food was given, diarrhea and vomiting occurred, just as in the case of Straub's dehydrated dogs. The vomiting and diarrhea in turn still further increased the dehydration.

We have observed a marked degree of anhydremia in infants suffering from pneumonia, from otitis media and from pyelitis. Some of these patients were vomiting and had been refusing part of their feedings. The toxic symptoms were especially marked in those patients showing considerable concentration of the blood.

The literature contains many references to the occurrence in newly-born infants of transitory fever, sometimes accompanied by toxic symptoms. The observations of Holt [33] and Crandall [34] on this condition has led to the view that the symptoms, in at least some instances, are the result of an insufficient intake of fluid. Recently much additional evidence in support of this hypothesis has been brought forward, notably by E. Müller [35] and by Rott.[36] The latter in a small series of cases demonstrated an increased desiccation of the body at the height of the fever.

33. Holt: Arch. Pediat. **12**:561, 1895.
34. Crandall: Arch. Pediat. **16**:174, 1899.
35. Müller: Berl. klin. Wchnschr. **47**:673, 1910.
36. Rott: Ztschr. f. Kinderh. **1**:43, 1911.

It is thus seen that desiccation of the body occurs in a great variety of conditions, and that the symptoms are essentially the same, no matter what the original cause. Diarrhea is by far the most frequent etiologic factor, but I do not feel that sufficient evidence has yet been introduced to warrant the assumption implied in the use of the term "alimentary intoxication" or "food poisoning." In the light of our present knowledge, the term "anhydremia" is accurately descriptive of the underlying factor and seems a suitable one to apply to all of these conditions, irrespective of the original cause.

If an infant suffering from diarrhea is given food, especially an excess of carbohydrate or fat, the diarrhea becomes worse and consequently the degree of anhydremia tends to become greater. If food is given to an individual who is anhydremic, even though diarrhea is not present, it is likely to result in diarrhea as has been previously mentioned. Furthermore, it has been shown by Straub in his experiments on dogs that anhydremic animals die sooner when food is administered than if they are completely starved, the explanation being that the soluble metabolites accumulating in the blood still further increase its osmotic pressure and decrease the available water reserve. We have in these facts adequate explanation of Finkelstein's observations that the giving of food increased the symptoms of his infants suffering from "alimentär intoxikation."

If the symptoms of the condition we are discussing are the result of anhydremia, they should disappear when a sufficient amount of fluid has been introduced into the body. In the case of a moderate degree of anhydremia resulting from insufficient fluid intake, the symptoms usually disappear rapidly after the administration of fluid by mouth. In the case of postdiarrheal anhydremia, the results are less striking. In the first place it is usually impossible to administer a sufficient amount of water by mouth. The water deficit of these patients is approximately the same as the amount of weight lost, that is, it may be from 300 to 1,500 gm., even in young infants. On account of the fact that vomiting and diarrhea are still present and that there is an excessive loss of water by evaporation as the result of increased metabolism chiefly of protein, water loss is so great that it is difficult to give enough water by mouth to keep the infant in water balance, to say nothing of introducing in a short period of time the extra amount required to make up for the deficit. Physiologic sodium chlorid solution may be given subcutaneously and a small amount intravenously, but these methods are only too often insufficient to restore normal conditions in the blood and tissues. By far the most efficient means of introducing water into infants of this type is by way of the peritoneal cavity. This procedure has been used to some extent in English clinics, but its great value seems to

have been little appreciated until Howland [37] made extensive use of it in his clinic. Since that time the method has become widely used and it has been the general experience that the intraperitoneal administration of large amounts of normal saline at frequent intervals is the most efficient therapeutic measure at present at our disposal. Inasmuch as these children have suffered a loss of mineral matter as well as of water and protein, there would seem to be a theoretical advantage in administering other salts in addition to sodium chlorid. Holt, Courtney and Fales,[5] on the basis of their metabolic studies, have recommended such a procedure. In our experience Ringer's solution is an excellent substitute for physiologic sodium chlorid solution. It is unnecessary to administer alkali to correct the acidosis unless this is of a severe grade, for when sufficient amounts of water are given the acidosis disappears, as the conditions which have led to its production are no longer present.

The loss of water from these infants has sometimes been so excessive that recovery is impossible, no matter what means are used. This it also has been found is the case in animals rendered anhydremic by various means. This is presumably on account of the destruction of body protein, which is known to occur. Lack of fluid intake rarely leads to such a severe degree of anhydremia that recovery is impossible unless at the same time there is an excessive loss of water from the body. Thus it has been demonstrated that animals subjected to complete food and water starvation may live for considerable periods of time providing there is no excessive loss of water by way of the gastro-intestinal tract or by evaporation. Sufficient water is produced in the metabolic processes to provide for the water balance. Any increased water loss from such animals results in the development of acute symptoms, ending in death.

Mention has already been made of the fact that many of the infants developing toxic symptoms following diarrhea are, to begin with, in extremely poor nutritional condition. The increased protein destruction during the period of anhydremia still further affects the nutrition so that although recovering from the effects of anhydremia the infants succumb as the result of the other condition.

In order to spare the protein destruction, the administration of carbohydrate is desirable. During the stage of acute symptoms glucose may to advantage be given intravenously, but always at such a rate and in such concentration that glycosuria does not occur. As glucose is completely metabolized, the water in which it is dissolved becomes entirely available. Glucose infusions, temporarily at least, increase the blood volume and this is an advantage. Glucose in isotonic

37. Blackfan and Maxey: Am. J. Dis. Child. **15**:19 (Jan.) 1918.

solution has been given intraperitoneally with excellent results, but in a certain number of instances this procedure leads to quite marked abdominal distention.

So much for therapy based on the conception of the pathogenesis of the condition. Curative measures can accomplish something, preventive ones much more. With an understanding of the nature of the disturbance, the problem of prevention is simplified.

Fortunately, relatively few infants suffering from diarrhea develop the severe toxic symptoms which have been recounted; it is usually those who have suffered from repeated attacks and whose nutritional condition is, as a result, far below par. Infants who are already in a condition commonly referred to as marasmus are those likely to finally succumb to the intoxication of anhydremia. It is this chronic condition of malnutrition which will next be discussed.

Anyone who has frequented the wards of an infant's hospital is only too familiar with the picture of these wasted infants. The condition exists in all degrees of severity, and it is often difficult to state just when it begins. An artificially fed infant may begin to vomit occasionally, the stools may vary from the normal, there may be constipation or more frequently repeated attacks of diarrhea, the weight fluctuates and then usually declines. If the feedings are increased diarrhea results, if decreased loss of weight continues. In other instances an infant may be thriving until some parenteral infection occurs which becomes chronic, for example, pyelitis or bronchitis. The weight progressively declines. Other infants fed on very dilute milk or insufficient amounts of proprietary foods never do well and the weight decline begins almost at birth. Ultimately, in each instance, the infant wastes to a skin covered skeleton. The paper thin skin has a gray pallor, the hands and feet are cold, the pulse slow, small and weak and the temperature often below normal, although heat production as measured in the calorimeter is markedly higher per kilo of body per day than that of normal infants. The blood is thin, pale and has a low hemoglobin and red cell content. The white blood count is often moderately increased. The urine is essentially normal in amount and in character except for a somewhat higher ammonia coefficient. From the metabolic standpoint, the most outstanding features of the condition are an inability to utilize food and a negative nitrogen and mineral salt balance. The picture is that of advanced starvation but often it is a starvation in the midst of plenty.

Various names, other than marasmus, have been applied to the condition. It is known as "infantile atrophy," "dekomposition" or "athrepsia." The latter term, applied by Parrot, is, perhaps, most accurately descriptive of the condition and, therefore, the preferable one.

No anatomic basis for the symptoms of this condition has been found, and here, as in the case of the intoxication states already discussed, it is necessary to assume an alteration in the chemical and physiologic processes of the body. The fact that some of the symptoms of the two conditions are identical and that one often merges into the other would lead one to suspect the presence of some common underlying factor operative in both. It, therefore, seemed worth while to apply the same methods previously used in the study of anhydremic cases.

Dr. J. F. Perkins and I began the study with the investigation of the protein content of the serum by the refractometric method. Very soon we were struck by the fact that the concentration of the protein in the serum of these infants was usually lower than the average for normal infants of the same age. The fact that there was also a diminution in the red blood cells and hemoglobin suggested that either the blood was hydremic by dilution with water or else that a destruction of both serum protein and cells had occurred. If the blood were hydremic there should be an increased blood volume, if destruction had occurred, a decreased volume. In order to determine which of these conditions was present, we made use of the vital red method for blood volume estimation.

In studying seven approximately normal infants under 1 year of age, two of whom were undernourished but gaining well, we found the average blood volume to be 9.1 per cent. of the body weight. The extreme variations were from 8.0 to 10.8 per cent. of body weight. Applying the same method to eleven athreptic infants, the blood volume was found to average 8 per cent. of the body weight, the extreme variations being from 4.8 to 10.4 per cent. The higher values in general were observed in those infants who might be considered as convalescing from the condition.

It is questionable if relationship to body weight is the best method of expressing blood volume when comparisons are to be made of individuals in different nutritional condition. Adipose tissue being relatively nonvascular, a thin individual of the same length and musculature should have a relatvely larger blood volume in proportion to body weight than a fat individual. The bodies of the marasmic infants that we studied were obviously almost free from fat. If the absolute blood volume of these had not been changed during the period of wasting the relation of blood volume to body weight should have been distinctly higher than under normal conditions. The very fact that the infants studied had a lower blood volume both absolutely and in relation to the body weight indicates that a very considerable destruction of the blood must have occurred along with the breakdown of other parts of the body.

As a result of the decrease in blood volume one would expect that volume flow would also be diminished. This was found to be regularly the case. The volume flow was often less than one-fifth, occasionally less than one-tenth of the normal. During convalescence the volume flow invariably increased.

An additional factor leading to such poor circulation is the condition of the heart muscle. Electrocardiographic tracings made on the infants of this series by Dr. Hugh McCulloch [38] showed occasionally, but by no means regularly, alterations from the normal complexes. The most marked variations were a low amplitude of all waves, and P and T waves being frequently isoelectric, a lengthened P-R interval and broad Q R S complexes. These variations were seen to disappear during convalescence. Whether these functional alterations are to be attributed to organic changes in the heart muscle or merely to an insufficient circulation through the intrinsic cardiac vessels is problematical. The rapid and complete recovery speaks for the latter supposition.

The decreased blood volume of these infants results in constriction of the arterioles and this leads to a piling up of corpuscles in the capillary blood. A large number of determinations of hemoglobin and red blood cells on venous and capillary blood from these infants invariably showed this corpuscular concentration in the capillary blood,[17] the increase being not infrequently as great as 20 per cent. over the venous blood. This fact may explain the gray color of the skin.

Arteriolar constriction may be considered a compensatory mechanism to maintain blood pressure at its normal height. In the case of anhydremia we have seen that the constriction is usually sufficient to maintain blood pressure but here there is the added factor of increased blood viscosity. In the athreptic infants the viscosity of the blood is not increased, and consequently the blood pressure sometimes falls below normal limits.

Sufficient has been said to provide the explanation for such symptoms of athrepsia as are identical with those of anhydremia. In the light of these facts, it is also easy to understand why an infant with a blood volume already diminished by atrophy should, when that volume is still further decreased by even a moderate degree of desiccation, readily develop the severe toxic symptoms characteristic of anhydremia.

In uncomplicated cases of athrepsia there is no increase in the concentration of the body fluids and no bar to the free evaporation of water, fever consequently does not occur. There is no increase in

38. McCulloch: Am. J Dis. Child. **20**: 1920. To be published.

the colloidal osmotic pressure of the blood, hence no diminution in the amount of urine secreted and no accumulation of urinary waste products in the body. Such acidosis as may occur is to be ascribed to causes other than the retention of acid products by the kidney. The acidosis is probably in part due to the diminished volume flow of the blood through the tissues and to a lesser extent to production of acetone bodies, the latter the result of partial starvation. Acidosis is, however, by no means a prominent feature of this condition.

We have no direct proof that the volume flow of the blood throughout the body is diminished to the same degree as in the extremities where it has been found possible to measure it. That some decrease of the blood to other parts of the body does occur, would seem likely, and it would not be unreasonable to suppose that such a diminution in the blood flow would seriously impair the functional activity of the gastro-intestinal tract, and interfere with the whole nutrition of the body. We know that following hemorrhage the nutrition suffers until the blood is restored; the same is apparently true in the case of athreptic infants, but in these infants there is, unfortunately, very little tendency to build up new blood. Transfusions have a temporary value only unless the underlying cause of body destruction is found and remedied.

So far we have discussed the effects of the breakdown of body tissues and but little has been said as to its cause. We know that simple starvation or a supply of food insufficient to cover the basal energy requirement of the body results in the destruction of the body itself in order to supply the fuel demands. The stored glycogen and fat are burned in preference to protein but when the fat and carbohydrate stores are exhausted a general consumption of protoplasm occurs as is evidenced by a markedly negative nitrogen and mineral salt balance. In a fair proportion of cases of athrepsia insufficient food intake is the obvious cause. Prolonged underfeeding either with natural or artificial food leads to the condition, and once it is fully developed the tolerance for food may be so low that it is impossible to give a sufficient amount to cover even the basal energy requirement.

It has been possible to duplicate exactly the condition of athrepsia in rabbits by prolonged underfeeding.[17] In such animals the blood volume decreased both absolutely and in proportion to the body weight and surface area. The volume flow of the blood decreased much more proportionately than the blood volume. The corpuscular count and volume diminished. When feeding was begun these animals maintained stationary weights for days even though given unlimited food. The blood volume was almost uniformly regained before any

weight increase was observed. Following this restoration of blood volume and volume flow there was a tendency for the weight curve to start upward. The majority of the rabbits ultimately made a complete recovery, but in a few the normal volume of the blood was not regained, and all of these did badly; the weight curve remained stationary and ultimately fell; all of these animals died. These experiments serve to emphasize the importance of blood volume in relation to nutrition, and lead one to suspect that the "period of repair" observed in the case of infants convalescing from athrepsia is a period during which the restoration of blood volume is occurring. Once this has been accomplished improvement is likely to be rapid and steady. If the blood volume is not regained the prognosis is poor.

An insufficient intake of food by mouth is by no means the only cause of athrepsia. In many instances the food given an infant is sufficient in calories but is either incompletely digested and absorbed or else it is not completely utilized by the body tissues after absorption.

Practically every infant normal at birth and free from infection will thrive when fed from the beginning on a sufficient amount of breast milk, but when the same number of calories or even the same proportion of fat, carbohydrate and protein are fed in the form of cow's milk a certain number of infants fail to gain and ultimately lapse into a state of severe malnutrition. There seems to be something about cow's milk which renders it unsuitable for these infants but there has been little unanimity of opinion as to just why cow's milk is unsuitable. The teleological explanation that cow's milk is made for the calf and not for the baby hardly suffices without further qualification.

At one time it was believed that the protein of cow's milk was the cause of the trouble but the modern conception, at least of the German school, seems to be that protein can do no harm, an idea which has not gone unchallenged. There are chemical differences in the fat of human and of cow's milk sufficient to account for some but not all of the differences in behavior of the two kinds of milk in the infant's body. The carbohydrates of human and of cow's milk differ only in quantity, but cow's milk cannot be made equivalent to breast milk by merely adding the extra 2.5 per cent. of lactose. The mineral salts of human and of cow's milk are quite different in character and amount, and Finkelstein believes this to be an important factor. According to him the whey salts of cow's milk may injure the intestinal mucosa and interfere with its functional activity, by way of decreasing its normal secretions and also by permitting the passage of harmful substances into the circulation. With an injured mucous membrane conditions are favorable for

abnormal bacterial activity in the intestine. The whey salts of cow's milk are in addition supposed to upset the normal mineral equilibrium of the body and lead to a loss of essential ash constituents.

In the attempt to demonstrate the harmfulness of the whey salts of cow's milk Meyer [39] performed his well known "whey exchange" experiments. He mixed the curds of cow's milk with the whey of breast milk and the curds of breast milk with the whey of cow's milk. Each of these mixtures were fed to infants convalescing from nutritional disturbances. On the basis of a limited number of experiments Meyer claimed to have shown that cow's milk curds in breast milk whey was well tolerated, whereas those infants fed on breast milk curds in cow's milk whey showed an increase in all the symptoms of a nutritional disturbance. He concluded from these experiments that cow's milk whey had a distinctly harmful influence. Such a definite, far reaching conclusion seems unjustified when we consider the differences in the caloric value of the two mixtures prepared by Meyer and also the different relationships between the organic constituents.

Within the past year Lichtenstein and Lindberg [40] repeated Meyer's experiments on a large number of infants and were unable to confirm his results or to substantiate his conclusions. They aptly state that the refutation of this theory amounts to "the removal of one of the cornerstones of Finkelstein's teaching structure."

There is a certain amount of good evidence that bacterial invasion of the upper intestine may occur in the case of infants suffering from nutritional disturbances. This has been demonstrated at necropsy by Moro [41] and others and by Bessau and Bossert [42] on living infants. This bacterial invasion may well be the factor in interefering with normal processes in digestion and absorption and hence with the actual amount of available food entering the circulation and brought to the body cells.

Abnormal bacterial growth in the upper intestine seems to be more frequent in infants fed on cow's milk but this is evidently not due to any greater bacterial content of the cow's milk as fed. Furthermore even apart from any bacterial factor, cow's milk often fails to satisfy the nutritional demands of certain infants.

There is one difference between breast milk and cow's milk which, it seems to me, has not been sufficiently emphasized, although it is mentioned in the literature. That is the high "buffer" value of cow's milk as compared with breast milk. By buffer value we mean a

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39. Meyer: Monatsh. f. Kinderh. **5**:361, 1906.
40. Lichtenstein and Lindberg: Jahrb. f. Kinderh. **89**:329, 1919.
41. Moro: Jahrb. f. Kinderh. **84**:1, 1916.
42. Bessau and Bossert: Jahrb. f. Kinderh. **89**:213, 269, 1919.

capacity to unite with relatively large amounts of acid or alkali without a great change in chemical reaction. If the same amount of hydrochloric acid is added to equal volumes of human milk and of cow's milk it is found that the acidity of the human milk expressed in terms of hydrogen ion concentration is far greater.

When milk enters the stomach of a normal infant gastric juice is secreted in such amount that the stomach contents ultimately reach a certain degree of acidity. This acidity expressed in terms of H-ion concentration averages about 1×10^{-5}, which is the optimum concentration for rennin action and is sufficient to markedly inhibit bacterial growth (Hahn [43]). The presence of acid on the gastric side of the pylorus initiates a reflex which allows for the passage of food into the duodenum. Here we know, from the work of Bayliss and Starling,[44] the acid acts on some substance in the mucous membrane which results in the production of the hormone "secretin," a substance capable of stimulating pancreatic and biliary secretion. Such is the normal course of events when the infant is fed on breast milk. Suppose, however, cow's milk instead of breast milk is fed. If the same amount of gastric juice is secreted, it is entirely insufficient to render the stomach contents acid to anywhere near the same optimum degree. To bring cow's milk to the optimum acidity of 1×10^{-5}, at least three times as much hydrochloric acid is required as in the case of human milk. (This may readily be demonstrated by titrating breast milk and cow's milk with diluted hydrochloric acid, using as an indicator neutral red which changes color at a hydrogen ion concentration of about 1×10^{-5}). We must, therefore, assume that the stomach secretes three times as much acid, or else that the optimum acidity is not reached. To secrete this extra amount is probably beyond the functional capacity of certain infants, yet if this amount is not secreted, bacterial inhibition and rennin action in the stomach occurs to only a slight degree. Without the passage of a sufficiently acid chyme into the duodenum, secretin formation and the hormone stimulation of the pancreatic and biliary secretion would necessarily be greatly diminished. In the light of these conditions, is it any wonder that certain infants fail to thrive on cow's milk which has been insufficiently diluted?

It is interesting to note that those foods which have been found empirically to be the best tolerated by athreptic infants are those which have a low buffer value or in which the buffer is already partly neutralized by acid. Breast milk, well diluted cow's milk with added carbohydrate, lactic acid milk and protein milk are examples.

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43. Hahn: Am. J. Dis. Child. **7**:305, 1914.
44. Bayliss and Starling: J. Physiol. **28**:325, 1902.

Some infants waste even when fed on considerable amounts of breast milk and when there are few gastro-intestinal symptoms. For some reason these infants are unable to make use of food. Congenital cardiac disease or chronic infections may be present, but occasionally no cause can be found, and we are compelled to make use of Czerny's term "abnormal constitution," to cloak our ignorance.

Athrepsia is essentially a condition of starvation dependent on any number of causes. But no matter what the cause, the end result is the same and that result is destruction of body tissue. In athrepsia, as the name implies, we have a clinical picture due to lack of nourishment. The obvious treatment is to supply food in such form as can be utilized by the body. The amount of food required is large for the basal energy requirement is high, and, in addition, much lost tissue must be replaced. Many of these infants fail to gain on less than 150 or 200 calories per kilo per day. The idea fostered by the German school that the condition is a result of food poisoning has no basis of fact and has resulted in much gross underfeeding of infants of this type. There is no good reason to believe that food, once it has passed the gastro-intestinal tract, is capable of harming these infants; diabetes, of course, being excluded. The feeding of an excess of indigestible food sets up an abnormal condition in the gastro-intestinal tract, so that less food is actually absorbed than when smaller amounts of more easily digested food is given.

Athreptic infants need calories; they also need protein, mineral salts, and the necessary accessory substances known as vitamins. Excessive amounts of protein are not required, certainly not more than 10 per cent. of the total caloric intake need be in the form of protein.

Fat is valuable chiefly for its vitamin content (fat soluble A). The digestive tract of these infants is, however, incapable of caring for excessive amounts of fat. Carbohydrates spare protein and are the most easily assimilated of all the foods. Carbohydrate must be relied upon to supply the greater part of the energy requirement of athreptic infants. It has been shown by Helmholz and Sauer [45] that the metabolic tolerance of these infants for sugar is exceedingly high. The problem is to give considerable amounts of carbohydrate without at the same time producing gastro-intestinal disturbance. Dextrin, because it is not readily fermented and on account of the fact that it has a high molecular weight and hence in solution exercises a relatively low osmotic pressure, is less likely to cause trouble in the gastro-intestinal tract than are some other sugars. Starch has some of the same characteristics as dextrin but is not quite so readily digested.

45. Helmholz and Sauer: Proc. Am. Pediat. Soc. **31**:256, 1919.

The actual percentage of carbohydrate in the food given is relatively unimportant. The percentage of carbohydrate which can be tolerated by the gastro-intestinal tract is dependent on the form of mixture in which it is fed, as well as upon the type of sugar. Mixtures of lactic acid whole milk containing as much as 10 per cent. of added carbohydrate are often very well tolerated by these athreptic infants.

Carbohydrate can be given in other ways than by mouth; for example, glucose can be administered intravenously or intraperitoneally. We have repeatedly given small infants more than an ounce of glucose a day by the latter method.

Even though a sufficient number of calories and an abundance of protein is supplied to these infants, they cannot build up protoplasm without mineral matter. The milk given may or may not supply the ash requirement. There may, therefore, be a theoretic basis for the administration of an extra amount of mineral matter. The French have indeed claimed beneficial results from subcutaneous administration of diluted sea water.

The accessory food factors or vitamins which are recognized as essential in the nutrition of the infant are all contained in milk, a food which necessarily forms the basis of the diet of these infants. The vitamin content of milk is known to be sufficient for the needs of normal infants, but recently the question has been raised as to whether or not the vitamin content of cow's milk is sufficient for the requirements of certain athreptic infants. Vitamins, especially the water-soluble B, have been added to the diet and according to Eddy and Roper [46] and Daniels and Byfield,[47] with excellent effect.

Mention has been made of the fact that the blood volume of athreptic infants decreases along with atrophy of the rest of the body. The blood volume decrease in itself, leads to severe symptoms, and seriously interferes with the nutritional processes. The blood volume tends to become restored through the period of repair, and is generally restored before the restoration of other parts of the body. Anything that would shorten this period of restoration should favorably influence the nutrition. Repeated blood transfusions and the intravenous injection of colloidal solutions, such as gum acacia, result in an increase in blood volume and volume flow, and are therefore theoretically indicated. I have repeatedly seen apparently good results from the use of such measures.

In the condition of athrepsia as in anhydremia, the therapeutic indications are clear, but only too often difficult or impossible of fulfillment. We have in one a clinical picture due to lack of water,

46. Eddy and Roper: Am. J. Dis. Child. **14**:189 (Aug.) 1917.
47. Daniels and Byfield: Am. J. Dis. Child. **18**:546 (Dec.) 1919.

in the other lack of nourishment; when these two essentials can be supplied and retained, recovery is possible, but only if the conditions have not existed for such a length of time that the body has been irreparably injured.

This discussion has been concerned with a consideration of some of the alterations in the physiologic and chemical processes occurring in the infant's body and with the methods of restoration of normal processes. It is interesting to note that those therapeutic procedures which are theoretically indicated in the light of recent work, are for the greater part exactly those procedures which have best stood the test of time and clinical experience.

STUDIES ON THE HEART IN NUTRITIONAL DISTURBANCES IN INFANCY*

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Infants who are suffering from nutritional disturbances and show signs of athrepsia may present various manifestations of circulatory derangements. Electrocardiograms have been made from a group of athreptic infants admitted to the St. Louis Children's Hospital, and it is my purpose to direct attention to certain observations made in the study of these cases.

Infants with athrepsia are in a state of partial starvation because the food they receive, for one reason or another, is not sufficient to supply the needs of the body tissues. An insufficient intake by mouth, an inability to completely digest and absorb food, or an inability on the part of the body tissues to completely utilize the food ingested are phenomena that lead to the development of this condition. Anatomic changes that might explain the symptoms associated with the condition have not been found in the body tissues, and it seems necessary to assume some alteration in the chemical and physiological processes and reactions of the body. Marriott[1] recently described the circulatory changes that occur in athreptic infants and brought out explanations for the various phenomena that occur in these infants. Briefly, the changes he describes are a slow, small and weak pulse; a surface temperature much below normal; a low hemoglobin and red blood cell count; concentration of the protein contents of the blood serum much lower than normal. The blood volume is much decreased, both absolutely and in relation to the body weight; the volume flow is often one-fifth, occasionally one-tenth of the normal; there is a constriction of the arterioles leading to a piling up of corpuscles in the capillary blood. The arteriolar constriction may be considered a compensatory mechanism to maintain blood pressure at its normal height; but despite this the blood pressure may fall below normal. He states that the evidence indicates that there is an increased tissue destruction throughout the whole body; the stored glycogen and fat are burned in preference to protein but when the fat and carbohydrate stores are exhausted, a general consumption of protoplasm occurs as is evident by a marked negative nitrogen and mineral salt balance.

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1. Marriott: Some Phases of the Pathology of Nutrition in Infancy, Harvey Lectures, Series 1919-1920, Am. J. Dis. Child. **20**:461 (Dec.) 1920.

These observations on infants have been substantiated by Utheim,[2] working in Marriott's laboratory. By prolonged underfeeding, the blood volume of rabbits was decreased both absolutely and in proportion to the body weight and surface area; the volume flow was decreased, and the corpuscular count and volume were also decreased.

Burge and Neill [3] studied the oxidative powers of various tissues in the bodies of animals before and after starvation by measuring the catalase content of those tissues. They consider that the catalase content of a tissue is directly proportional to the amount of oxidation in that tissue. The heart, which is not autolyzed during starvation, shows a normally high catalase content which is not decreased during starvation. While that of the fat and skeletal muscles which are autolyzed during starvation, is greatly decreased and at the end of periods of starvation these tissues have an exceedingly low catalase content.

Electrocardiograms from infants showing various nutritional states have been made previously by many observers. In those infants with a severe loss of water and body weight, the curves often have shown abnormal forms of the ventricular complexes. Noeggerath [4] studied the electrocardiograms made from infants that were prematurely born, or who were suffering from disturbances of nutrition or from infection. He observed many curves with abnormal ventricular complexes and also noticed that severely atrophic infants show a slowing of the pulse due to a sinus bradycardia and not to a disturbed cardiac mechanism. He concludes that the electrocardiogram is of no value in estimating the degree of function of the heart in such infants, nor is the method of value in determining the prognosis; that its usefulness is restricted to the demonstration and analysis of disturbances of cardiac mechanism.

Czerny [5] examined the hearts of athreptic infants by roentgenograms and found that the area of the heart shadow is much decreased in size. The condition exists independently of a loss in water content of the infant and it is most pronounced immediately preceding death. He is inclined to think that the heart is incompletely filled during systole, due partly to the decrease in total blood volume, but most likely to a disturbed action of the diaphragm.

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2. Uthheim: Study of the Blood and Its Circulation in Normal Infants and Infants Suffering from Chronic Nutritional Disturbances, to be published in Am. J. Dis. Child.

3. Burge and Neill: The Effect of Starvation on the Catalase of the Tissues, Am. J. Physiol. **43**:58, 1917.

4. Noeggerath, C. T.: Elektrokardiogramme Schwächliche Säulinge, Ztschr. f. Kinderh. **6**:396, 1913.

5. Czerny, Ad.: Zur Kenntnis der Zirkulationsstörungen bei Akuten Ernährungsstörungen der Säuglinge, Jahrb. f. Kinderh. **80**:601, 1914.

Fletcher and Hopkins [6] studied the relation of acids, particularly lactic acid, to the activity of amphibian muscle, and conclude that the presence of acid products depends on how favorable the conditions that exist in the muscle are for oxidative processes. When the oxygen supply is adequate, there is no accumulation of acid products, but when factors are present which diminish the oxygen supply, the acid is increased and can be removed only slowly and with difficulty. Their experiments show that lactic acid formed in muscle from various causes follows this rule and its disappearance is dependent on the oxygen supply.

Burridge [7] has shown that the rate of propagation of contraction in the frog's ventricle may be delayed by the addition of inorganic acids in sufficient strength to the fluid with which the heart was perfused. He states further that after treatment of the heart with a sufficient strength of acid to cause the heart to stop beating, by replacing such acid solution by Ringer's solution containing sodium bicarbonate, spontaneous beating will be resumed but with markedly delayed conduction of the impulse through the ventricles.

Mines [8] concludes from his experiments that certain changes in the electrocardiogram which result from increased frequency of the heart beat may be due to changes in the hydrogen ion concentration in some region of the muscle. He states that it is only when the hydrogen ion concentration is raised above a certain value that the effect will appear. After a long pause the hydrogen ion concentration is certainly lower than after a period of activity. Oxidative removal of lactic acid is a slow process and during the pauses between successive contractions of the heart, the removal is certainly not complete. A long pause will mean more complete removal.

The work of Fletcher and Hopkins, of Burridge and of Mines offers experimental proof for the observations made by Robinson [9] in this laboratory. He reports cases in which there were abnormalities in the form of the electrocardiogram due to faulty conduction of the cardiac impulse through the ventricles. This faulty conduction, he considers, depends on what has been termed "functional fatigue" rather than on anatomic lesions involving the intraventricular conducting system. He cites examples in which derangement of the ventricular

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6. Fletcher and Hopkins: Lactic Acid in Amphibian Muscle, J. Physiol. **35**: 247, 1907.

7. Burridge: Propagation of Contraction in the Frog's Heart, J. Physiol. **45**: 6, 1912.

8. Mines: On Dynamic Equilibrium in the Heart, J. Physiol. **46**:349, 1913.

9. Robinson: The Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med. **24**:422 (Sept.) 1919.

conduction has resulted from lack of time for conduction recovery after a ventricular contraction. In one case distinct improvement in intraventricular conduction followed slowing of the heart rate when longer diastolic pauses were present. The rate of recovery of conduction was observed also in this case to become more rapid with improved circulatory efficiency. He concludes, in part, that "lesions causing an insufficient blood supply to the ventricles are responsible for the presence of acid metabolites, which accumulate whenever the oxygen supply to the muscle is inadequate."

CLINICAL OBSERVATIONS

A group of sixteen infants who showed moderate or severe degrees of athrepsia were studied. Electrocardiograms were made on admission to the hospital and at subsequent times when the evidence indicated a material change in the clinical condition. Curves that were made within a period of twelve hours preceding death were not included since it was felt that any change in the electrocardiogram at that time might be due to the fatal cardiac failure rather than to the condition we are studying. Below are the curves selected from two of the cases which indicate functional changes in the cardiac mechanism.

CASE 1 (Children's Hospital No. 14454).—The patient was admitted to the hospital, July 21, 1919, for an acute intestinal disorder. He has been a normal baby, except for improper feeding, up to about one week previous to admission, when vomiting and diarrhea set in. The baby responded quickly to hospital care and was discharged well one week later. He began vomiting and having diarrhea again at home and returned to the hospital August 4. He was suffering then from severe athrepsia and anhydremia. Electrocardiogram 2760 was made shortly after his admission. Again he improved and was doing well when he developed ileocolitis and pyelitis. Electrocardiogram 2827 was made during this period. His lower resistance and nutrition were not sufficient to withstand the infection and he died September 24.

Electrocardiogram 2760 (Fig. 1), made August 17, shows no evidence of abnormal muscle preponderance. Q R S time is 0.080 second, not abnormal. The complex is normal in form, except that the waves are low in amplitude. This is particularly true in Lead I. The P wave is not present in Lead I and III; it is low in Lead II. The T wave is not present in Lead I and III; it is abnormal in form in Lead II. Ventricular rate 95.7 per minute. P R time, 0.200 second, is a distinct delay in an infant.

Electrocardiogram 2827 (Fig. 2), made September 4, shows distinct improvement in the cardiac condition as compared with Electrocardiogram 2760. The Q R S times is 0.080 second, but the amplitude of the waves is much increased and now seems normal. The T waves are well formed in all leads, the change being particularly noticeable in Lead I. The P waves likewise are easily made out in all leads. Ventricular rate 103.8 per minute. P R time, 0.160, a faster time than Electrocardiogram 2760.

Interpretation: The decrease in the time for auriculoventricular conduction, the faster heart rate and the improvement in the form of the Q R S, and T and P complexes, coincident with the decrease in the signs of athrepsia, would indicate an improvement in the function of the heart.

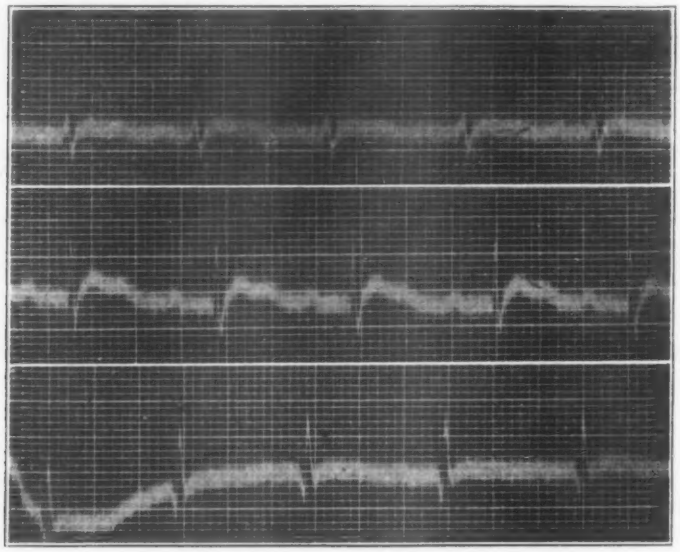

Fig. 1.—The Q R S complex is normal in form but the waves are low in amplitude. The P R time is 0.200 second, being slightly delayed. Ventricular rate, 95.7 per minute.

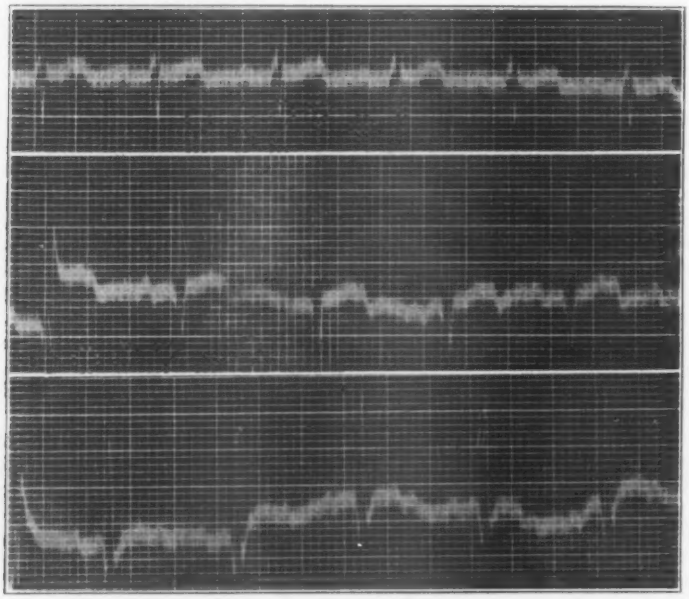

Fig. 2.—The amplitude of the Q R S complex is much increased. Ventricular rate, 103.8 per minute. The P R time is 0.160 second, the conduction time being much faster.

CASE 2 (Children's Hospital No. 15063 and 15248).—Patient was admitted to the hospital, Jan. 22, 1920, suffering from marked degrees of athrepsia, anhydremia and acidosis. The findings in the study of the circulation were in accord with those described by Marriott. It is not shown how long she had been ill or what the previous feedings had been. She was discharged from the hospital in fair condition February 9. Electrocardiogram 3457 was made the day after her admission when her condition was at its worst. She was readmitted March 5 because of a return of her previous nutritional disturbance. Electrocardiogram 3711 was made at this time. Shortly after this admission she developed an acute otitis media which was followed by an erysipelas and she died.

Electrocardiogram 3457 (Fig. 3), made January 23, shows no evidence of abnormal muscle preponderance. The Q R S time is 0.060 second, not abnormal. The complexes are abnormal in form, particularly in Leads II and III. In Lead II the down stroke of the R wave is notched and in Lead III it is broadened out. Further, the waves are low in amplitude. The T waves are absent in all three leads. Ventricular rate, 150 per minute. The P R time is 0.160, an abnormal delay in an infant with such a ventricular rate.

Electrocardiogram 3711 (Fig. 4) was made March 7. As in Case 1 these curves show distinct improvement in the cardiac function. Q R S time is not shortened nor is the form changed, but the amplitude is much greater. The T waves are well formed though R T time, which is 0.240 second, seems much delayed. Ventricular rate, 138 per minute. The P R time is 0.120 second, a distinct improvement in the auriculoventricular conduction.

Interpretation: This curve was made at the time when the degree of athrepsia was not so marked and the patient seemed to be improving. It is probable that there was some improvement in the heart function.

In explanation of the alterations in the electrocardiogram reported by Robinson,[9] he states that sclerosis of the coronary vessels furnishes the condition for the increased production of acid metabolites and it also tends to delay their removal. Myocardial lesions, such as fibrosis would, perhaps, also tend to produce these effects by lessening the efficiency of the blood supply to the cardiac tissue. In athreptic infants the heart muscle and coronary vessels on examination have not shown any recognizable anatomic fibrosis or sclerosis. But the marked decrease in the blood volume and delay in blood flow with low protein content would certainly result in a deficient supply of oxygen to the body tissues, with a resulting increase in hydrogen ion concentration. These changes would furnish the conditions under which alterations in the cardiac mechanism might occur. Alterations have been found as shown in the examinations made by previous observers and in the two cases reported above. The alterations in these two cases are not extensive but they are distinct enough to show that a profound influence has been exerted on the heart. In spite of the protective measures that have been set up to spare the heart, they have broken down. There has been a delay in impulse conduction from auricles to ventricles and when the nutrition of the body improved this abnormal delay disappeared and the impulses passed freely from auricles to ventricles. Coincident with this the form of the T waves was much improved and the amplitude of the Q R S complex was increased.

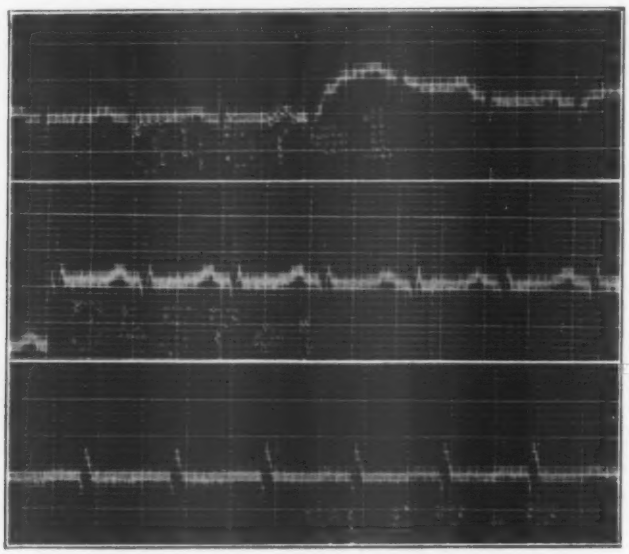

Fig. 3.—The Q R S waves are low in amplitude. Ventricular rate, 150.0 per minute. The P R time is 0.160 second.

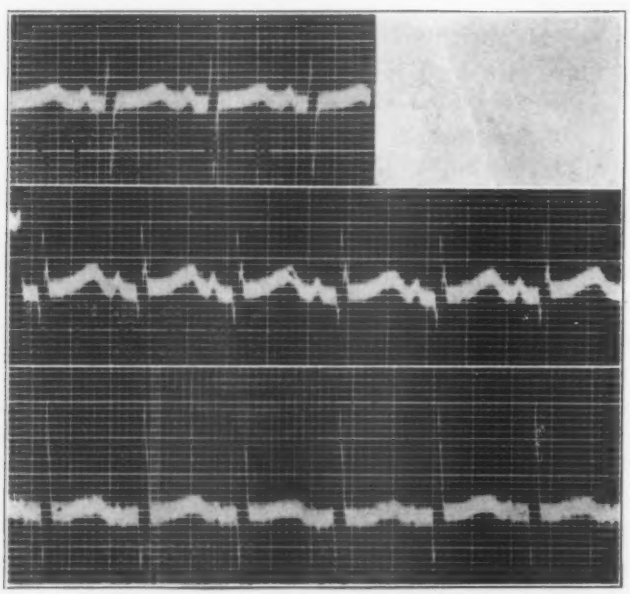

Fig. 4.—The amplitude of the Q R S waves are much increased. Ventricular rate, 138 per minute. The P R time is 0.120 second, being much faster than in Figure 3.

The changes described occurred in infants who were markedly athreptic, as evidenced by the other examinations on the circulation, but other infants suffering from athrepsia of just as severe a type have failed to give evidence of any disturbance in the electrocardiogram. Nor does the length of time that the nutritional disturbance has existed seem to be a factor in the production of functional changes in the heart. It is not to be expected that these changes would occur constantly for we must consider that several important factors are present in athreptic infants which delay the failure of circulation in the heart itself. The observations on volume flow, total volume and protein content of the blood have been made on the peripheral circulation of the body surface and especially in the extremities. It is both conceivable and probable that these same changes make themselves felt in the internal organs of the body, though possibly not to the same extent.

Phenomena that occur in one area of the circulation need not occur to the same degree or of the same kind in all the circulatory areas. In a pathologic state in which the circulation is altered to such an extent as in these athreptic infants, it is hardly conceivable that the internal organs can escape wholly some alteration in their circulation; truly, in mild cases no change may occur, but in the moderate and severe cases the profound changes observed in the surface area must spread to the deeper structures. Furthermore, it is probable that nature makes every attempt to provide primarily for the vital structures, the heart, brain and internal organs, and will endeavor to protect those structures from damage as long as possible. If the volume of blood is diminished, if the oxygen content is low, the blood will be diverted as much as possible by surface vasoconstriction into the circulation of those organs whose functional activity is essential to life. By withdrawing fluid from the rest of the body tissues, more fluid may be made available for the heart and other internal organs. If sufficient food for body needs is not received the glycogen and fat in the body tissue is used up and finally the tissue protein. The organs which are most essential for life, such as the heart and central nervous system, are preserved as long as possible, while organs which are relatively nonessential, waste away. It is probable even then that the heart is one of the last structures in the body to feel the effect of tissue destruction, one of the last structures in which the oxygen supply is diminished.

The hearts of infants suffering from athrepsia may be further protected by the decrease in heart rate so commonly observed. The more activity in the heart muscle, the more rapid the rate and the greater the need for oxygen. In experimental study it is found that

when the surface areas become depleted of fluids and the blood vessels constricted to prevent further loss of heat, the animal becomes quiet and thus prevents muscular activity in those areas involved. The same phenomena occur in the heart. Functional fatigue appears to prevail if the oxygen supply is diminished and subsequently the cardiac mechanism is deranged. A slow heart rate acts as a compensatory mechanism to protect the heart muscle.

In making electrocardiograms from athreptic infants, we have found in most instances that the body resistance is very high and for this reason it is difficult to obtain satisfactory curves. The skin surface is dry and attempts to produce erythema and a moist skin with a high conductivity by rubbing with hot salt solution before applying the electrodes, is almost uniformly unsuccessful. It is common to find the body resistance as high as from 2,000 to 3,000 ohms, often higher. During convalescence in the favorable cases, coincident with the improvement in the circulatory conditions the body resistance is again lowered and the electrocardiogram may be obtained with the same ease as in a normal infant. Due to the withdrawal of fluid to other parts of the body the water content of the subcutaneous tissues is so much reduced that the electrical conductivity is lowered.

In some incompleted experiments we have attempted to produce alterations in the cardiac mechanism and in the form of the ventricular complex of animals. Up to the present time we have not succeeded in doing so.

We have no evidence that the alteration in the cardiac mechanism is dependent on structural change in the conducting tissue or the heart muscle. We think they are functional in nature resulting from an insufficient circulation of oxygen through the coronary vessels. Czerny's observation that the area of the heart shadow is decreased in size is probably due to incomplete filling of the heart chambers and coronary vessels.

CONCLUSIONS

1. Electrocardiograms were made from a group of sixteen athreptic infants, and in the case of two of these infants, alterations of cardiac mechanism were observed. The alterations consisted of a delay in auriculoventricular conduction, and changes in the form of the Q R S complex.

2. As an explanation of these disturbances we offer a suggestion that they are the result of alterations in the blood and body tissues in these infants suffering from nutritional disorders. It is probable that the changes which have taken place in the blood result in a deficient supply of oxygen to the heart, with incomplete or delayed removal of metabolic products (acid metabolites) from the cardiac tissue.

3. When improvement takes place in these athreptic infants the alterations in cardiac mechanism disappear. Measures adopted to relieve the nutritional disturbance seem to be the rational treatment for the cardiac condition as well.

4. We have not observed any phenomena indicating heart failure in these infants.

INFANTILE SPINAL PROGRESSIVE MUSCULAR ATROPHY (WERDNIG-HOFFMANN)

REPORT OF A CASE WITH NECROPSY FINDINGS *

E. J. HUENEKENS, A.B., M.D., AND E. T. BELL, M.D.
MINNEAPOLIS

In 1891, Werdnig,[1] a neurologist of Graz, gave the history, with necropsy findings, of a peculiar disease, which he termed early infantile progressive spinal muscular atrophy. This is his description:

> In a family without neuropathic taint, two or more children, who had been well up to that time, become sick about the tenth month of life, without fever, convulsions or other signs of infection. The disease begins very gradually, in that they cannot use their legs as well as formerly, the children never learn to walk and cannot stand without help. There is atrophy and paralysis of the muscles of the back and pelvic girdle (marked in the gluteal muscles), but especially in the quadriceps. The disease, in a chronic, progressive, centrifugal and symmetrical course, involves the shoulder girdle, neck and throat muscles, later the muscles of the thigh and arm, then the leg and forearm and last the muscles of the hands and feet. There is atrophy of the muscles en masse; there is no hypertrophy or pseudohypertrophy. Bulbar symptoms, fibrillary twitchings and secondary contractures may be present. There is marked flaccid paralysis with complete loss of the tendon reflexes and a partial loss of the skin reflexes, sitting up is very difficult or impossible. There is lordosis of the lumbar spine. There is no pain or tenderness anywhere, nor objective disturbance of sensation. Sphincters are normal. Mental development is good. There is extreme atrophy of the muscles, but not of the subcutaneous fat. There is involvement of the muscles of respiration and the disease runs a quick fatal course; in the mildest cases, within several years. The pathologic findings are primary symmetrical disease of the spinal cord, consisting of atrophy of the anterior horn cells, without evidence of any inflammatory process; a marked degeneration of anterior nerve roots; secondary simple atrophy of the muscles with more or less marked increase of nuclei; in places, degenerative atrophy and lipomatosis of the muscles.

These observations were confirmed by Hoffmann,[2] of Heidelberg, in 1893. Since that time, about fifteen typical cases have been reported, with only a few necropsy reports.

The English neurologists, especially Beevor[3] and Batten,[4] have contributed largely to our knowledge of this disease. In this country

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* Read before the Section on Diseases of Children at the Seventy-First Annual Session of the American Medical Association, New Orleans, April, 1920.

1. Werdnig: Arch. f. Psychiat. **22**:706, 1891.
2. Hoffmann: Deutsch. Ztschr. f. Nervenh. **3**:427, 1893.
3. Beevor: Brain **25**:85, 1902.
4. Batten: Brain **33**:433, 1910.

the only report on record is that of Bliss,[5] of St. Louis, who reports three cases in one family, but no necropsies were made.

In 1900, Oppenheim [6] described a new syndrome, which has been given various names, including amyotonia congenita and Oppenheim's disease, but the best term seems to be amyotonia congenita (Oppenheim). He described it as: "congenital, but not hereditary nor familial; present in full bloom at birth, consisting of a hypotonia of most of the muscles of the body, with absence of tendon reflexes and no reaction of degeneration, and a tendency to progressive improvement."

The pathologic anatomy was described as being primarily in the muscles, though Oppenheim did not exclude a secondary degeneration of the anterior horn cells.

Spiller,[7] of Philadelphia, was the first to report a necropsy of a typical case of this condition, and he found no spinal cord involvement. Councilmann and Dunn [8] and Leriboullet and Baudouin [9] report the same necropsy findings, but practically all the other reported necropsies of both the Werdnig-Hoffmann and Oppenheim types show the same spinal cord involvement originally reported by Werdnig.

Marburg,[10] of Vienna, gives the following differential diagnosis:

Amyotonia Congenita	Werdnig-Hoffmann
1. Congenital.	1. Acquired in early life.
2. Usually single, rarely familial.	2. Usually familial.
3. Generalized hypotonia.	3. Localized atrophies, beginning in the pelvic region and spreading.
4. Atrophy masked, not grossly apparent.	4. Atrophy easily recognized and apparent.
5. Tendon reflexes absent.	5. Proportional to the atrophies.
6. Stimulated by electricity or the hypotonic reaction given. (Farad. O., Galv. plus.)	6. Reaction of degeneration.
7. Course with improvement.	7. Progressively worse, a mere skeleton at 4 to 5 years.

However, the fact that the pathologic findings in muscle and spinal cord are the same in both types of cases, and the further fact that there are all shades of gradation between the typical Oppenheim and Werdnig-Hoffmann types, leaves it open to doubt whether they are not extreme types of the same disease.

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5. Bliss: J. Nerv. & Ment. Dis. **44**:108, 1916.
6. Oppenheim: Monatschr. f. Psychiat. u. Neurol. **8**:232, 1900.
7. Spiller: Univ. Penn. Med. Bull. **17**:342, 1904.
8. Councilmann and Dunn: Am. J. Dis. Child. **2**:354 (March) 1911.
9. Leriboullet and Baudouin: Bull. et mém. Soc. méd. d. hô. de Par. **26**:1162, 1909.
10. Marburg, quoted by Spiller: Arbeit. a. d. Neurol. Instit. Wien. **19**: 1912.

Collier and Wilson [11] are very firm in their conviction that they are two distinct entities and most other writers on the subject are inclined to agree with them.

Rothmann,[12] however, considers the two diseases identical. After an exhaustive consideration of the whole question, he comes to the following conclusions:

1. The disease picture of amyotonia rests, at least in the majority of cases, anatomically on a degeneration of the anterior horn cells, which may lead even to a complete disappearance of these elements.
2. Between amyotonia and Werdnig-Hoffmann disease we can have, according to our present material, all gradations with identical anatomic findings, so that we can draw no sharp distinction between the two disease groups.
3. From the whole group of early infantile spinal progressive muscular atrophy the congenital cases can be separated. Further, we can differentiate as amyotonia those cases which have come to a standstill and have a possibility of improvement, from spinal atrophy which becomes progressively worse and ends fatally.
4. We can have gradations between amyotonia congenita with involvement of the lower brain nerve roots and the Moebius "Kernschwund" with accompanying involvement of the cord.

At the International Congress of Medicine in London,[13] 1913, in a discussion of the relation of the myopathies, Batten and Spiller inclined to the same conclusion as Rothmann.

Careful survey of the literature shows that there are all clinical gradations between the two diseases and no definite pathologic distinction. All the cases of Werdnig-Hoffmann type and all but three cases [7, 8, 9] of the Oppenheim type show atrophy and disappearance of the anterior horn cells. The pathologic changes in the muscles are identical in the two diseases.

No sharp differentiation can be made between amyotonia congenita and the Werdnig-Hoffmann type on the ground that the former is congenital and the latter acquired in early life. Reference to the accompanying table (Cases 7, 8, 9, 16, 17, 22, 28 and 29) will show eight cases which were typically of the Oppenheim type, except that the disease was not present at birth. Neither can a definite distinction be made on the ground that the Werdnig-Hoffmann type is familial and that the Oppenheim type occurs singly. The table shows ten cases (Cases 14, 18, 20, 21, 34, 35, 39, 40, 41 and 42) in which otherwise typical Oppenheim cases are familial.

The points given by Marburg [10] in the differential diagnosis, relating to the extent of the atrophy, the condition of the reflexes and the electrical reactions, are so inadequately reported in the literature

11. Collier and Wilson: Brain **31**:1, 1908.
12. Rothmann: Monatschr. f. Psychiat. u. Neurol. **25**:161, 1909.
13. Batten and Spiller: Tr. Internat. Congr. Med., Sec. 11, Neuropath. pp. 2-125.

that they offer no basis for differentiation. The point that amyotonia tends toward improvement, while the Werdnig-Hoffmann type becomes progressively worse, offers no clear distinction. Reuben,[14] in a very complete report of 136 more or less typical cases of amyotonia, says of the course and prognosis:

> In a great majority of the congenital cases the progress is one of slow but gradual improvement; however, in not a single case was there complete recovery; . . . in a small minority (thirteen cases) there was no improvement noted at any time; in these cases there was progressive deterioration up to death. In some of the cases in which there was progressive improvement there were noted long periods in which the condition was stationary. . . . The prognosis as to recovery is absolutely bad; there is no record of complete recovery in a single case. Of eighty-four in which the final outcome is stated, forty-five are known to have died.

The two cases in one family, reported by Bibergeil,[15] deserve special consideration. His second case is undoubtedly a typical case of Oppenheim's disease, except that it probably started late. His first case tended more toward the Werdnig-Hoffmann type; it was familial, had fibrillary twitchings, there was muscle atrophy, involvement of the facial and of the hypoglossal nerves, and differing degrees of hypotonia on both sides of the body. Against the diagnosis of the Werdnig-Hoffmann type is the tendency to improvement and absence of reactions of degeneration.

REPORT OF CASE

In connection with this controversy, a report of our case is of interest. The family history is very important and is given in full.

Father and mother are living and well, no history of syphilis, no miscarriages. The first child (male), aged 8, is in very good health. The second (female) died at 3 months. The mother had felt very weak fetal movements up to three weeks before birth, but they ceased altogether after that. The mother had remarked at the time that she "wondered what was wrong because the child did not move." The mother did not have the care of the child until it was 2 weeks old, but at that time she noticed that it did not move its legs and arms, but could move its toes and fingers and that it had difficulty in nursing and swallowing. The condition was so marked that a physician was consulted. The child seemed to improve in that it was able to bend its knees slightly which it had not done previously. At 3 months of age the baby "took cold" and died in three days, probably from bronchopneumonia. The mother considered the child better just before death than at 2 weeks.

The third child (Borghild) is the subject of our report. A fourth child (male) has since been born, is now 1 year old and normal in every way, both physically and mentally.

Three first cousins of the mother living in Norway, present an interesting history. One did not walk until 3 years of age, but is now well and strong; a second had some condition which started when she was 1 year of age. She

14. Reuben: Arch. Int. Med. **20**:657 (Nov.) 1917.
15. Bibergeil: Ztschr. f. d. Ges. Neurol. u. Psych. **22**:411, 1914.

did not walk very well, "limped on both feet," fell down very suddenly without warning, but without loss of consciousness. These falls would occur two or three times a day, and she was not able to walk more than one or two blocks at a time. She had something resembling contractures of the hands, is now an invalid and in bed most of the time. A third had exactly the same condition, but not so severely, still falls down occasionally, but is able to be up and about; she also holds her hands in a peculiar fashion. These two girls are now about 30 years of age. This history of the cousins was obtained from the mother, who went to school with the girls for a number of years.

Borghild J., the subject of this report, was a full term infant, breast-fed up to the fourth month, when allaitment mixté was instituted. The mother felt fetal movements all through the latter half of pregnancy. The child appeared normal from birth up to the age of 6 weeks, moved legs and arms and sucked fingers, and when lying prone tried to raise its head. At 6 weeks, the baby was vaccinated against smallpox, but the vaccination was unsuccessful, no scar remaining. At this time, the mother noticed that the child gradually grew weaker in its movements, especially of the hips; this gradually grew worse until death, the legs hanging limp when the child was held up. The arms were also involved, but the baby could lift a spoon to its mouth up to the last three weeks of life, and would try to grasp at a ball suspended over the crib almost up to the time of death. At 4½ months, with slight help (one finger supporting the chin) could hold up head, but at the fifth month this had become impossible. The mother first noticed difficulty in breathing at 4 months, the child would seem about to choke from the amount of mucus in the throat. At the same time it began to have difficulty in nursing, seemingly on account of the mucus and would gasp for breath. The baby had always had a weak voice from the first few days of life, this gradually grew weaker until it was reduced to a soft wail.

The baby was brought to one of us (E. J. H.) at the age of 5 months.

Physical Examination.—Weight, 6,200 gm., underdeveloped, undernourished, fontanel rather wide open, no craniotabes, musculature over entire body very flabby, almost doughy in feeling, skin pale. There was moderate dyspnea, with expansion of the alae nasi at each inspiration. There was extreme deformity of the chest, a modified Harrison's groove, the upper half of the chest being extremely narrow and the lower half, below the attachment of the diaphragm, flaring markedly. The chest was rather tympanitic and no abnormal dulness was noticed. The heart tones were clear. Abdomen, rather large and dependent, the liver palpable 3 cm. below the costal margin; spleen not palpable. Palmar and plantar surfaces clear. Knee jerks absent. Because of the difficult respiration and the deformity of the chest the possibility of some mediastinal condition was suspected and a roentgenogram of the chest was made. Shortly afterward, while being nursed, the baby went into collapse and seemed about to die. However, it revived after fifteen or twenty minutes, was taken home and a trained nurse was installed for several days.

This nurse was able to confirm many points of the mother's story; she reported in addition peculiar wavelike contractions of the trunk muscles, starting at the pectorals and spreading downward over the abdomen. The nurse described it as resembling the reverse peristaltic wave of pylorospasm, only more pronounced. The temperature was normal, but the child would have frequent attacks of slight collapse.

The collapse in my office seriously interfered with a further complete examination. Owing to the parents' objections, the electrical reactions could not be taken, nor a blood examination made. The child was seen four or five times during the following month, but no change in the condition was noted, except that the mother noticed

adductions of the fingers of both hands, somewhat resembling tetany, though the muscles of the hands were not rigid. The child seemed mentally normal up to death.

The child died suddenly at the age of 6 months.

NECROPSY REPORT

External Appearances.—Body is 70 cm. long and fairly well nourished. There is a marked abnormality of the chest, both lateral surfaces being concave. There is a slight concavity in the anterior median line of the thorax, but not nearly so marked as the depression of the lateral surfaces. The inferior border of the thorax is outstanding, due to the depression of the other parts of the chest. The anterior fontanel measures 4 cm. transversely and 5 cm. anteroposteriorly. Other fontanels are closed. Circumference of head, 44.5 cm. Muscles are atrophic, those on the backs of the thighs being especially shrunken. Body has been embalmed. Slight lividity is present. No edema, cyanosis or jaundice. Pupils are 4 mm. in diameter and equal.

Peritoneal Cavity.—Embalming fluid is found in peritoneal cavity. There are no peritoneal adhesions. Marked atrophy of pectoral muscles. Mesenteric lymph nodes are prominent. Diaphragm extends to fourth rib on right side, to fifth rib on left side. Appendix shows no gross lesions.

Thymus.—Greatly enlarged, extending to the diaphragm on the right side of the median line and to 1 cm. of the diaphragm on the left side. It is distinctly lobulated and weighs 29.5 gm.

Pleural Cavities.—No fluid and no adhesions.

Pericardial Cavity.—Contains no excess fluid and no adhesions.

Heart.—Normal size. Chambers are not dilated. Valves, endocardium, and musculature show no lesions. Root of aorta shows no lesions.

Lungs.—Markedly collapsed. Crepitation is greatly reduced, especially in anterior and upper portions of lungs. No nodules are palpable. Cut surfaces show very little air. No pus. No excess of fluid.

Spleen.—Weighs 25 gm. Capsule is smooth and clear. Cut surfaces show prominent lymphoid follicles.

Liver.—Weighs 230 gm. Capsule is smooth and clear. Cut surfaces show no special markings. Gallbladder and ducts show no lesions.

Gastro-Intestinal Tract.—No gross evidence of disease.

Pancreas.—No lesions; lobules are distinct.

Suprarenals.—Greatly reduced in size, the right weighing 1.5 gm., the left 1.8 gm. The cut surfaces show no changes, except decreased thickness of the layers.

Kidneys.—Left weighs 20 gm.; right weighs 21 gm. External surfaces smooth. Cut surfaces show no special markings. Pelves are clear.

Bladder and Genital Organs.—No pathologic conditions found.

Aorta.—No gross lesions.

Lymph Nodes.—Fairly prominent throughout body, but not larger than is usual at this age.

Thyroid.—Weighs 3.6 gm.

Head.—No lesions found in the soft tissues of the scalp. Temporal muscles are atrophic. Meninges of brain show no evidence of disease. Sinuses of dura are clear. The cerebral convolutions show no evidence of atrophy. The brain is cut in coronal sections; no gross evidence of disease found. Portions reserved for microscopic examination.

TYPICAL AND ATYPICAL CASES OF WERDNIG-HOFFMANN TYPE

Case	Author	Necropsy	Age When First Seen	Onset	Diagnosis Reported	Course	Familial	Outcome
1	Werdnig[1]	Cord involvement	3 yrs.	10 mos.	W-H.*	Worse	Les	D. 5 yrs.
2	Werdnig[18]	Cord involvement	15 mos.	10 mos.	W-H.	Worse	Yes	D. 6 yrs.
3	Hoffmann[2]	Cord involvement	4 yrs.	10 mos.	W-H.	Worse	Yes	D. 5 yrs.
4	Hoffmann[2]	No necropsy	2¾ yrs.	10 mos.	W-H.	Worse	Yes	L. 3½ yrs.
5	Hoffmann[2]	No necropsy	.....	6-12 mos.	W-H.	Worse	Yes	D. 1½ yrs.
6	Hoffmann[2]	No necropsy	9 mos.	5 mos.	W-H.	Worse	Yes	D. 15 mos.
7	Wimmer[19]	No necropsy	16 mos.	9 mos.	W-H.	Worse	No	Unknown
8	Haberman[20]	Cord involvement	18 mos.	5 mos.(?)	O.	Worse	No	Died
9	Hoffmann[21]	Cord involvement	1 yr.	7 mos.	W-H.	Worse	Yes	D. 3 yrs.
10	Hoffmann[21]	No necropsy	9 mos.	9 mos.(?)	W-H.	Worse	Yes	?
11	Sorgente[22]	No necropsy	27 days	Birth	O.	Worse	Yes	D. 30 days
12	Sorgente[22]	No necropsy	5 days	Birth	O.	Worse	Yes	D. 20 days
13	Beevor[3]	Cord involvement*	5 wks.	Birth	O.	Worse	Yes	D. 8 wks.
14	Collier and Wilson[11]	No necropsy	5 yrs.	Birth	O.	Better	Yes	D. 3 yrs.
15	De Villa[23]	No necropsy	3 yrs.	Birth	O.	Better	Yes	
16	Skoog[24]	No necropsy	22 mos.	14 mos.	O.	Better	No	L. 22 mos.
17	Ritter[25]	Cord involvement	15 mos.	5 mos.	W-H.	Worse	No	D. 16 mos.
18	Porter[26]	No necropsy	3 yrs.	Birth	O.	Better	Yes	?
19	Batten[4]	Cord involvement	4 wks.	Birth	W-H.	Worse	No	D. 4½ wks.
20	Batten[4]	Cord involvement	5 wks.	Birth	W-H.	Worse	Les	D. 8 wks.
21	Batten[4]	No necropsy	4 mos.	Birth	W-H.	Worse	Yes	Died
22	Batten[4]	No necropsy	6 mos.	4 mos.	W-H.	Worse	No	Died
23	Batten[4]	Cord involvement	8 mos.	Birth	W-H.	Worse	No	Died
24	Batten[4]	Cord involvement	3½ yrs.	Birth	W-H.	Worse	No	D. 4 yrs.
25	Collier and Holmes[27]	Cord involvement	5 yrs.	Birth	O	Better	No	D. 7 yrs.
26	Collier and Holmes[27]	No necropsy	3½ yrs.	Birth	O	Worse	No	Died
27	Boudouin[28]	Cord involvement	4 mos.	Birth	O.	Worse	No	D. 5 mos.
28	Marburg[10]	Cord involvement	3 mos.	6 wks.	O.	Worse	No	Died
29	Thomson and Bruce[29]	Cord involvement	?	1 yr.	O.	Worse	No	D. 8 yrs.
30	Griffith and Spiller[30]	Cord involvement	15 mos.	Birth	O.	Better	No	D. 2½ yrs.
31	Councilmann and Dunn[8]	No cord involvement	6 mos.	3 wks.	O.	Worse	No	D. 6½ mos.
32	Bliss[5]	No necropsy	25 mos.	10 mos.	W-H.	Worse	Yes	D. 2½ yrs.
33	Bibergeil[15]	No necropsy	5½ yrs.	1 yr.	W-H.	Better	Yes	Lived
34	Bibergeil[15]	No necropsy	3½ yrs.	1 yr.	O.	Better	Yes	Lived
35	Foot	No necropsy	3 mos.	Birth	O.	Worse	Yes	D. 4 mos.
36	Reuben[14]	No necropsy	6 mos.	Birth	O.	Better	Yes	D. 10 mos.
37	Reuben[14]	No necropsy	10 wks.	Birth	O.	No improvement	Yes	D. 4 mos.
38	Reuben[14]	No necropsy	3½ mos.	Birth	O.	Better	Yes	Died
39	Pearce[32]	No necropsy	22 mos.	Birth	O.	No improvement	Yes	L. 22 mos.
40	Pearce[32]	No necropsy	22 mos.	1 yr.(?)	O.	Better	Yes	L. 22 mos.
41	Pearce[32]	No necropsy	7 mos.	Birth	O.	No improvement	Yes	L. 8 mos.
42	Pearce[32]	No necropsy	7 mos.	Birth	O.	No improvement	Yes	L. 8 mos.

W-H. signifies Werdnig-Hoffmann; O. signifies Oppenheim.

* Other cases in same family started 4 weeks, 6 months 6 weeks.

18. Werding: Arch. f. Psychiat. **24**: 76, 1894.
19. Wimmer: Arch. f. Psychiat. **42**: 1907.
20. Habermann: Am. J. M. Sc. **139**: 383, 1910.
21. Hoffmann: Deutsch. Ztschr. f. Nervenh. **10**: 292, 1897.
22. Sorgente, quoted by Collier and Wilson: La Pediat. **24**: 355, 1916.
23. De Villa: Arch. de méd. d. Enf. **19**: 137, 1916.
24. Skoog: J. A. M. A. **55**: 364, 1910.
25. Von Ritte: Jahrb. f. Kinderh. **59**: 224, 1904.
26. Porter, quoted by Spiller: Brain **30**: 75, 1913.
27. Collier and Holmes: Brain **32**: 269, 1909.
28. Baudouin: Semana méd., May 22, 1907, p. 241.
29. Thomson and Bruce, quoted by Batten: Brain **20**: 536, 1897.
30. Griffith and Spiller: Am. J. M. Sc. **142**: 165, 1911.
31. Foot: Am. J. Dis. Child. **5**: 359 (Sept.) 1913.
32. Pearce, N. O.: Personal communication: To be published.

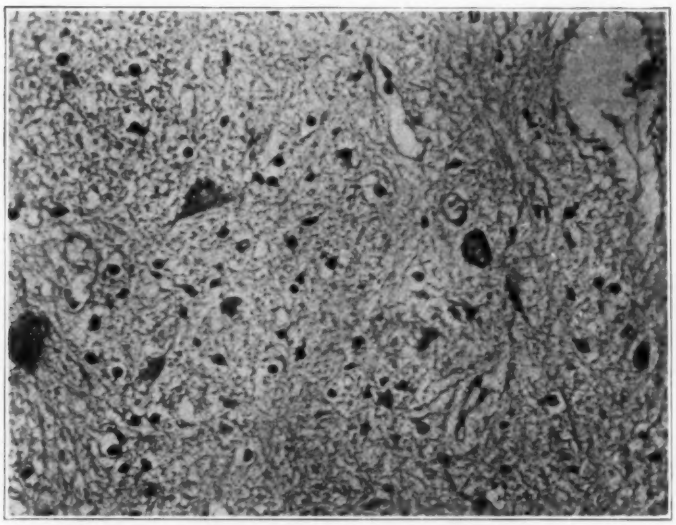


Fig. 1.—Area from the anterior horn in the thoracic cord. The nerve cells are greatly reduced in number, and many of them show extreme atrophy and disintegration.

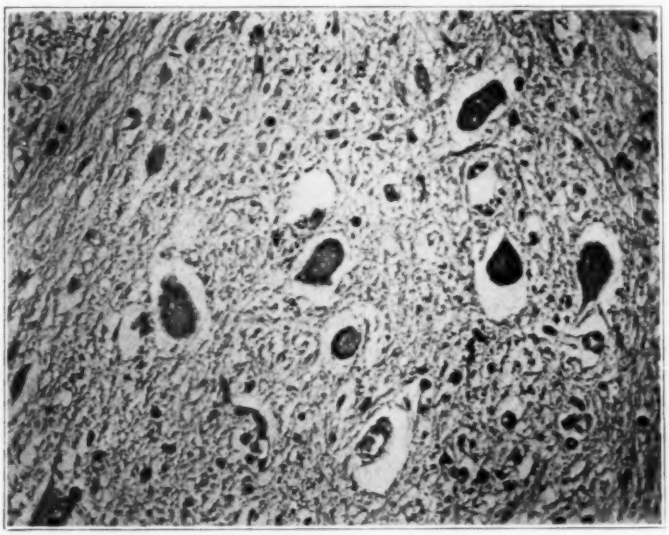


Fig. 2.—Area from Clark's column in the thoracic cord. (Same magnification as Figure 1.) The cells of this group are only slightly affected. The spaces around the cells are probably artefacts.

Fig. 3.—Area from biceps femoris muscle (low magnification).

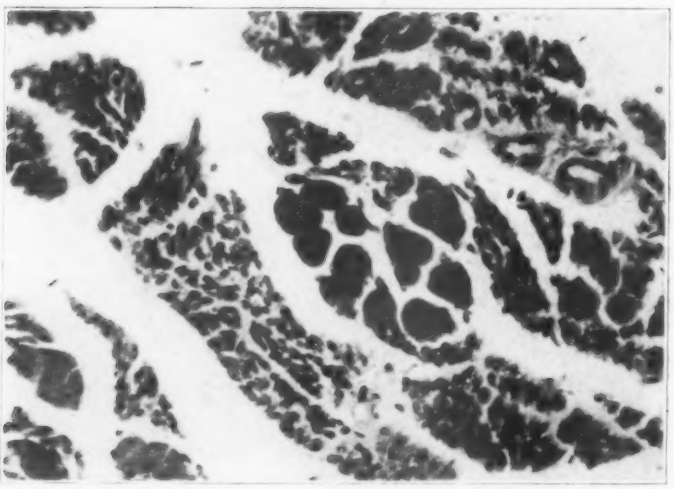
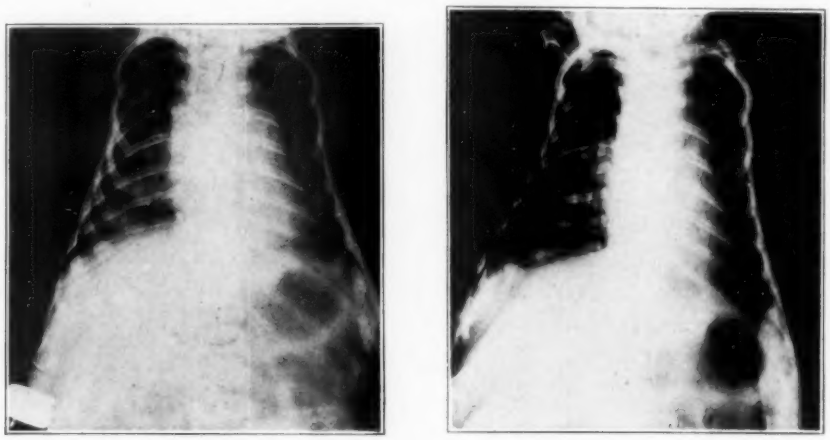


Fig. 4.—Higher magnification of an area from Figure 3.

Spinal Cord.—Meninges show no gross evidence of disease. No abnormalities in the shape of the cord. No certain evidence of disease noted on transverse sections observed with the naked eye.

Muscles.—Muscles of back and ileopsoas muscles also show marked atrophy.

Microscopic Examination.—Spinal cord: There are no changes at any level of the cord in the posterior horns. In the cervical portion there is no certain decrease in the number of nerve cells in the anterior horns, but there are a few very small cells, apparently atrophic. In the thoracic cord there is a striking decrease in the number of nerve cells in the anterior horns; and the few cells present are usually very small. Only an occasional cell of normal size is to be seen (Fig. 1). The cells in the intermediate area between the anterior and posterior horns are atrophied, but not noticeably reduced in number. The atrophy is not symmetrical, being more extensive on one side of the cord than on the other. In the lumbar cord the lesions are about the same as in the thoracic. There are no lymphocytic infiltrations or hemorrhages in any part of the cord. Sections stained by Weigert's myelin sheath method show a moderate reduction of medullary sheaths in the fasciculus gracilis.



Figs. 5 and 6.—Roentgenogram showing characteristic deformity of chest and enlargement of thymus.

Sections of the psoas and biceps cruris muscles were studied. The changes in each of these muscles consist in a marked atrophy of nearly all the muscle fibers. Some fasciculi are composed entirely of atrophic fibers; others contained both normal and atrophic fibers. Occasionally a fasciculus is seen which is composed mainly of normal fibers (Figs. 3 and 4). The difference in size between the normal and the atrophic fibers is very striking. The normal fibers average about 4 microns in diameter, while the atrophic fibers vary from 0.5 to 1.5 microns. The measurements were made from paraffin sections.

On microscopic examination the lungs show marked atelectasis. The heart, spleen, liver and kidneys show normal histologic structure.

The thymus shows a simple hyperplasia. There is a thinning of the cortex and medulla of the suprarenals.

Diagnosis.—Spinal muscular atrophy; atelectasis of lungs; hypertrophy of thymus.

Comment.—The enlarged thymus is of interest for two reasons: first, because roentgenograms taken at the first examination showed a broad shadow in the upper thorax, but it is not typical of an enlarged thymus (Figs. 5 and 6); second, because other authors (Pollak,[16] Councilmann and Dunn [8]) report a similar condition. Smith,[17] reporting the visceral findings on Spiller's case, shows enlargement of Hassal's corpuscles.

The unusual features of this case are: it is not only familial, but evidently hereditary (family history of muscular dystrophy). The second important feature is that the first baby, which died at the age of 3 months, presumably was a true case of amyotonia congenita, since the condition was probably present at birth and tended to improve up to the time of death. The second case was a typical Werdnig-Hoffmann. It was not present until the child was 6 weeks of age, grew progressively worse and was familial. With the exception of the doubtful cases of Bibergeil,[15] these are the only cases on record of the existence of a probable Oppenheim's and Werdnig-Hoffmann's disease in the same family.

CONCLUSION

From a review of the literature and our own case, the conclusion seems justified that amytonia congenita (Oppenheim) and infantile spinal progressive muscular atrophy (Werdnig-Hoffmann) are extreme types of the same disease; that they are probably both related to the group of myopathies represented by Erb's juvenile form of muscular dystrophy and the hereditary form of Leyden and Moebius.

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16. Pollak: Arch. f. Kinderh. **53**:373, 1910.
17. Smith, Allan J.: Am. J. M. Sc. **142**:165, 1911.

CONGENITAL ATRESIA OF THE ESOPHAGUS

WITH REPORT OF A CASE *

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Congenital anomalies of the upper digestive tract are not as infrequent as is generally supposed. Plass [1] found 204 references in the literature and was able to verify 137 cases from the original articles. Besides these he found thirteen cases which he could not verify on account of incorrect references or inaccessibility of the original article. He does not include any references later than 1917, and since that date several cases have been reported. Cautley,[2] Apfel,[3] Crowdy [4] and Huntington [5] have each described one case, while Brenneman [6] reported four new cases. In a discussion of Griffith's paper read before the American Pediatric Society in 1908, Dr. Putnam of Boston reported a case which has escaped notice.

Cautley's article contains a large number of references and in order to bring the literature up to date, I have appended to the references quoted in this paper a list of Cautley's references which do not appear in the Plass biography,[7] several of which I have been able to verify from the original paper. There are now reported more than 150 cases not including about twenty-eight cases which could not be confirmed.

The case which I desire to report is typical of the great majority of these malformations.

REPORT OF CASE

Dr. C. A. Pitts of Albany called me in consultation May 4 to see a baby which he had delivered May 2. The mother was a primipara and the labor was

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* Read before the American Pediatric Society, May-June, 1920.

1. Plass: Johns Hopkins Hosp. Rep., 1919.
2. Cautley: Brit. J. Child. Dis. **14**:1 (Jan.-March) 1917.
3. Apfel: New York M. J. **108**:108 (July 20) 1918.
4. Crowdy: J. M. Research **38**:469 (July) 1918.
5. Huntington, Young and Foot: Boston M. & S. J. **180**:354 (March 27) 1919.
6. Brenneman: Am. J. Dis. Child. **16**:143 (Sept.) 1918.
7. Heath: Complete Absence of the Esophagus, London Med. Gaz. **26**:543; Tiedeman: Anatomie Kopfloser Missgeburten (Quoted by Schoeller); Kathe: Double Esophagus, Virchows Arch. **190**:78, 1907; Cannan and Berg: Atresia. Arch. gén. de med., p. 79, 1826; Edington: Glasgow M. J. **80**:16, 1913; Guillemet: Gaz. méd de Nantes **24**:576, 1906; Keith: A Demonstration of Fourteen Specimens from Museums of London Hospitals. (Probably individual cases reported elsewhere.) Brit. M. J. **1**:301, 1910; Pagenstecher: Siebold's J. f. Geburtsh. **19**:112, 1830; Richter: Surg., Gyn. & Obst. **17**:397, 1913; Schwalbe: Morph. der Missbildungen des Menschen und der Tiere, p. 777, 1912.

uneventful. The baby was well nourished and strong. It was observed when the baby was placed on the breast that the milk returned through the nose and thick mucus stained with dark brown material came out of the nose and mouth. Whenever she attempted to nurse she would have violent attacks of coughing and choking and expel both the milk and this thick brown stained mucus. The same thing would occur when she was given water in a bottle. Meconium was freely passed by the bowels and urine was voided normally. The temperature was elevated, from 102 to 103 F., and the chest was filled with coarse moist râles, but there was no dullness. The child appeared to be hungry and suckled vigorously when placed on the breast, but after a few swallows the milk came out of the nostrils. A small catheter was passed by the mouth, but it met with an obstruction, and on further pressure the catheter doubled up and the end appeared in the mouth. A smaller catheter passed through the nose met with the same result. It was decided to have a roentgenogram made to determine whether surgical procedure would relieve the condition. The plates made by Dr. Dinegar showed that the esophagus ended in a culdesac and that surgery offered no relief. Figure 1 illustrates the distance which the catheter could be passed and Figure 2 shows the culdesac filled with a barium mixture. These, so far as I can find, are the only roentgenograms which have been taken of this condition.

The diagnosis was simple. An operation was not advised. Two days later the baby died.

NECROPSY REPORT

The postmortem examination was made at the Bender Laboratory, May 6, 1920, by Dr. Ellis Kellert.

Frances H., age 4 days, 15 hours postmortem; body weight, 3,120 gm.; body length, 55 cm.

The body is that of a fairly well nourished, new-born female infant. Rigor mortis is absent, and there is marked lividity in the dependent parts. Externally the body is normal.

Peritoneal Cavity.—The surfaces are normal and smooth, moist and glistening. The mesenteric lymph nodes are not enlarged. The appendix is normal. The cecum is distended with meconium. There is no displacement nor abnormality of the abdominal viscera.

Pleural Cavities.—Normal.

Pericardial Cavity.—Normal.

Heart.—Normal on inspection.

Lungs.—They are slightly collapsed and deeply congested, with pale and dark red mottlings. The right middle lobe is somewhat atelectatic. On the left side the upper lobe is divided into two portions simulating three lobes to the right lung. Numerous small irregular hemorrhagic areas are present throughout. The thoracic organs and organs of the neck are removed in toto, together with the stomach.

Gastro-Intestinal Tract.—The tongue and mouth appear to be normal. The esophagus, from the tongue to a point 6 cm. below the uvula, presents a somewhat thickened wall and ends abruptly in a blind pouch. The extremity is rounded, and does not even show a fibrous connection with the lower esophagus. The stomach is normal in size and is filled with blackish-green material resembling meconium. The lower portion of the esophagus is present and in passing a probe upward it emerges through the larynx. On dissection, the lower half of the esophagus is found to be normal in appearance. It opens directly into the trachea at the bifurcation, the walls of the esophagus blending imperceptibly with those of the trachea. The trachea is filled with blood, mucus and material

Fig. 1.—Catheter is introduced as far as possible.

Fig. 2.—Barium in culdesac shows its size and extent.

from the stomach. The pylorus is slightly thickened, but there is no obstruction. The small and large intestines are normal throughout. The sigmoid is very mobile and free.

Genital Organs.—Normal.

Spleen.—Normal in size, shape and appearance.

Liver.—Normal.

Kidneys.—Normal. The lobulations are very distinct.

Suprarenals.—Normal.

Anatomic Diagnosis.—Atresia of esophagus. Congenital defect, with lower esophagus terminating in the trachea at the bifurcation. Early bronchopneumonia. Anomaly of left lung—three lobes.

The main points of interest in this case are the absence of a fibrous connection between the culdesac and the lower portion of the esophagus, the three lobes of the left lung and no other anomalies in the gastro-intestinal tract.

A very complete classification of esophageal malformations was made by Ballantyne [7a] from a study of the literature.

1. Complete absence of the esophagus, its place being taken by a muscular band stretching from the pharynx to the cardiac end of the stomach.
2. Termination of the esophagus in a simple culdesac.
3. Termination of the esophagus in a culdesac, the lower rudiment of the canal communicating with the trachea or bronchi.
4. Tracheo-esophageal fistula, the esophagus being otherwise normal.
5. Membranous obstruction of the esophagus.
6. Presence of esophageal diverticula.
7. Duplicity of the esophagus.

This case comes under the third type, which comprises more than 75 per cent. of all the reported cases. This points to some common embryonic origin. Zeit [8] has shown that the separation between the digestive and respiratory tract is complete at the end of the first month of fetal life. These anomalies are probably the result of an insufficient or faulty separation through lack of proper septum formation.

The first recorded case of malformation of the esophagus is one reported by Durston [9] in 1670. This case is referred to by Cautley but the original article is not available in this country. It was a case in which there was a culdesac and union between the two portions of the esophagus by a fibrous cord. Blasius [10] published a case of double esophagus in 1674.

7a. Ballantyne: Antenatal Pathology of the Embryo, 1905, p. 462.

8. Zeit: J. M. Research **27**:1277, 1912.

9. Durston: Collert. Acad. Part. etrang., 1670, Tab. II, p. 283. (This reference was quoted by Crozer Griffiths.)

10. Blasius: Observata anat. pract. in homine. Ludg. Batav. et Amster., 1674, Tab. XV, Fig. 6.

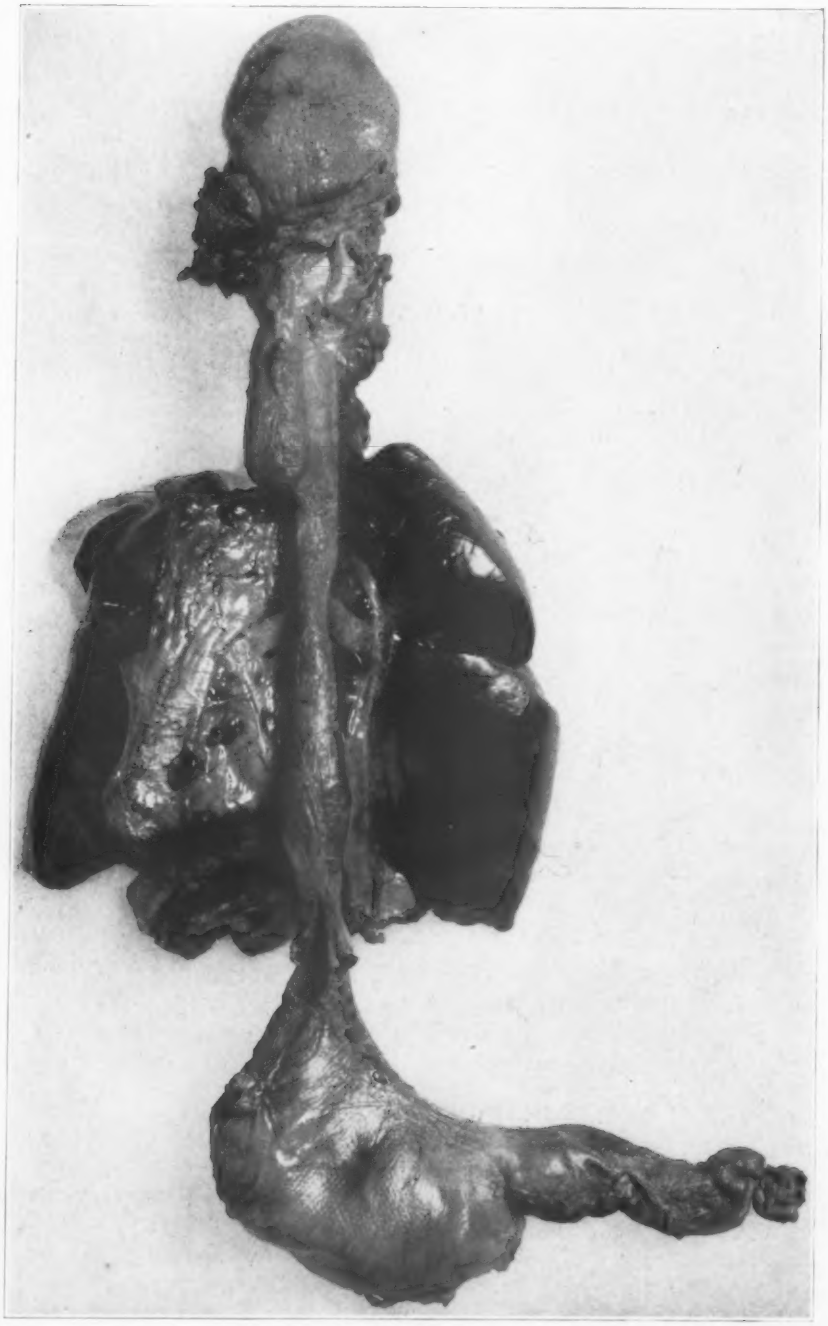

Fig. 3.—Anatomic relations of culdesac and trachea.

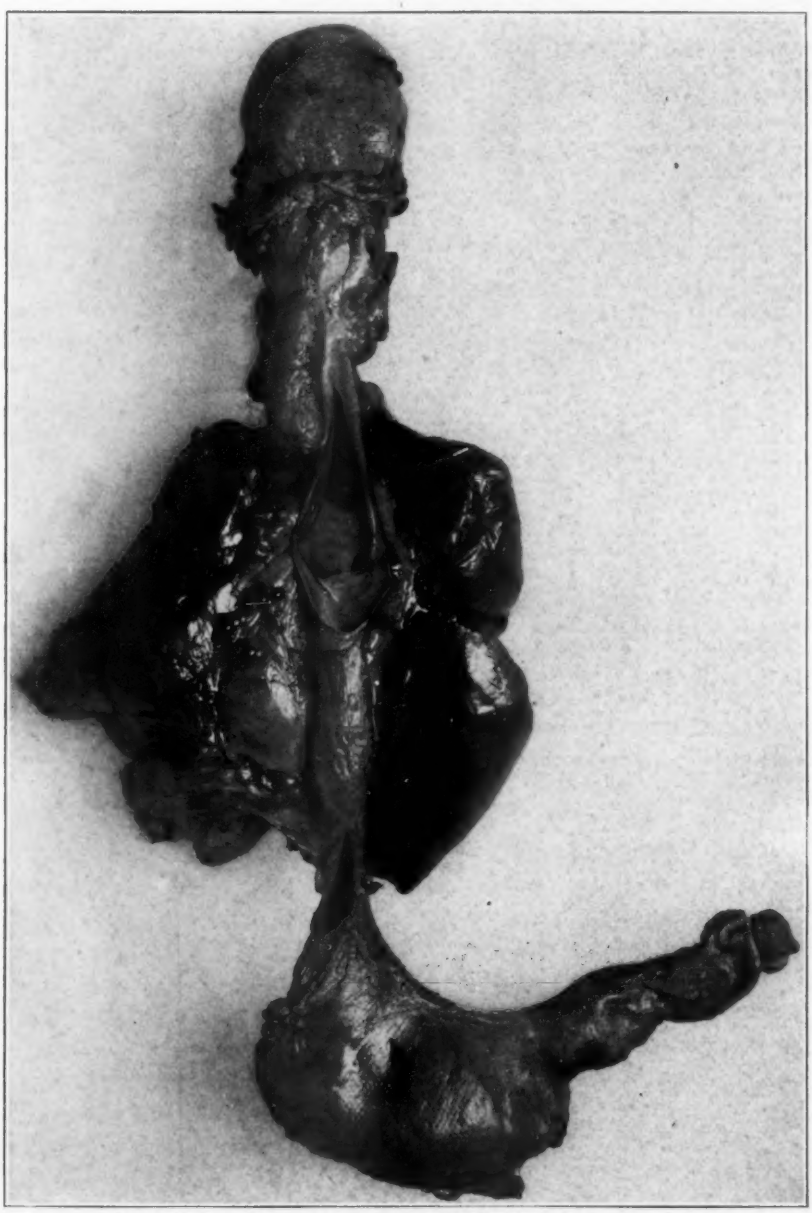

Fig. 4.—Opening is shown of lower part of esophagus in the trachea and absence of connection between upper and lower parts.

A very typical case was reported by Thomas Gibson[11] in 1696. Plass quotes this case, which is so quaintly described that it bears repetition.

About November, 1896, I was sent for to see an infant that could not swallow. The child seemed very desirous of food and took what was offered it in a spoon with greediness, but when it went to swallow it was like to be choked, and it fell into a struggling convulsive sort of a fit upon it. It was very fleshy and large and was two days old when I was called to it, but the next day it died.

The parents being willing to have it opened, I took two physicians and a surgeon with me. On opening the abdomen first, the guts had some of the meconium still in them, though the child had gone two or three times to stool. The stomach had in it a pretty deal of a slimy sort of liquid (or jelly rather), somewhat like thick (strained) water-gruel. I shall not mention observations upon other parts of the abdomen, as being not to our present purpose.

Then we cut open the thorax and taking out the gullet (with the windpipe, lungs, etc.) continued to the stomach. Then we made a slit in the stomach and put a pipe in its upper orifice, and blowing, we found the wind had a vent, but not by the top of the gullet. Then we carefully slit up the back side of the gullet from the stomach upwards, and when we had gone a little above half way toward the pharynx we found it hollow no further. Then we began to slit it open from the pharynx downwards, and it was hollow till within an inch of the other slit, and in the imperforate part it was narrower than in the hollowed. This isthmus (as it were) did not seem to ever have been hollow, for in the bottom of the upper and to top of the lower cavity there was not the least print of any such thing, but the parts were here as smooth as the bottom of an acorn cup.

Then searching which way the wind had passed when we blew from the stomach upwards, we found an oval hole (half an inch long) on the fore side of the gullet opening into the aspera arteria, a little above its first division, just below the lower part of the isthmus above mentioned.

Recent literature does not contain any clearer or more accurate description of this condition.

DR. THOMAS GIBSON

A few words concerning Dr. Thomas Gibson may be of interest in this connection. He was born in 1647 and died in 1722. He was a general practitioner, but wrote the most popular book on anatomy of that day, the first edition appearing in 1682, and the sixth edition in 1703. This book was entitled "The Anatomy of Humane Bodies Epitomized," and a copy of the sixth edition is in the Surgeon General's Library in Washington. Dr. Gibson was "physician-general" to the British Army in 1718-1719. An interesting sidelight on his character is found in the diary of Thomas Hearne of Oxford under date of September 8, 1717, which shows that he married a granddaughter of Oliver Cromwell.

Sept. 8. On Saturday (Sept. 5) came to Oxford two of the daughters of Richard Cromwell, son of Oliver Cromwell, protector, one of which is married to Dr. Gibson, the physician, who writ the Anatomy; the other is unmarried.

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11. Gibson: The Anatomy of Humane Bodies Epitomized, Ed. 6, 1703.

They are both Presbyterians, as is also Dr. Gibson, who was with them. They were at the Presbyterian meeting-house in Oxford on Sunday morning and evening; and yesterday they, and all the gang with them dined at Dr. Gibson's, provost of Queen's College, Oxford, who is related to them, and made a great entertainment for them, expecting something from them, the physician being said to be worth 30,000 libs. They went from Oxford after dinner.

The recognition of these cases is not difficult and the passage of a small catheter establishes the diagnosis, which can be further confirmed by the roentgen ray.

Treatment is most unsatisfactory. No case has recovered or been benefited in the slightest way by either surgical or medical treatment. Brenneman [6] gives a full discussion of surgical methods which may be employed and his conclusion is that "surgical procedures have so far only served to end more quickly a hopeless situation."

OBSERVATIONS ON THE CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE

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In the transition from intrauterine to extrauterine life few organs of the body are more affected than the stomach. The change influences many characters of the organ's morphology, and the position, the mass, the finer structure, and particularly the capacity are rapidly modified and adjusted to the new conditions and functions of postnatal life.

The changes in gastric capacity in this period of transition have not been studied very intensively. As early as 1856 Guillot [1] published some data regarding physiologic gastric capacity in the first few days of extrauterine life and this was followed somewhat later by a more extensive study by Bouchaud.[2] Since that time further information on the subject has been published by Hillebrand,[3] Kruger,[4] Ssnitkin,[5] Cammerer,[6] Tuley,[7] Jaschke,[8] Landois [9] and others. The figures presented in most of these studies are not extensive, and are usually incidental to more general studies of metabolism in the neonatal period. Much of the early work is no longer of more than historic value because the observations were made under conditions

1. Guillot, N.: De la nourrice et du nourrisson, Union méd., 1852, p. 61.
2. Bouchaud: De la mort par inanition et études experimentales sur la nutrition chez le nouveau-né, Thèse, Paris, 1864.
3. Hillebrand, F.: Untersuchungen über Milchzufuhr und über die Jodkaliumausscheidung des Saüglings, Arch. f. Gynäk. **15**:453, 1885.
4. Krüger, G.: Ueber die zur Nährung Neugeborener erforderlichen Milchmengen mit Rücksicht auf die Gewichtsveränderungen der Kinder, Arch. f. Gynäk. **7**:59, 1875.
5. Ssnitkin, N.: (The Quantity of Breast-Milk Consumed by Sucklings), Allg. med. Centr. Ztg. **45**:317, 1876.
6. Cammerer, W.: Der Stoffwechsel eines Kindes im ersten Lebensjahr, Ztschr. f. Biol. **14**:383, 1878.
7. Tuley, H. E.: Observations on the Capacity of the Stomachs of Infants Under Ten Days of Age, Arch. Pediat. **10**:423, 1893.
8. Jaschke, R. T.: Neue Erfährungen in der Technik der Ernährung sowie zur Physiologie und Pflege des Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **35**:60, 1912.
9. Landois, F.: Zur Physiologie des Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **22**:194, 1905.

which no longer obtain in modern infant feeding. Regarding anatomic capacity in this period, we have still less accurate information, the only extensive series of measurements being that of Alliot [10] on newborn children.

It has been pointed out recently that, during the greater part of the suckling period, there exists a fairly definite and constant relation between the anatomic capacity of the stomach, as determined postmortem, and the physiologic capacity as ascertained by weighing the child before and after feeding.[11] And it has been found that the capacity of the stomach increases at a very definite rate in early life despite the numerous fluctuations due to differences in physical constitution and to varying physiologic factors. It is the purpose of the present paper to trace the changes which these measures of gastric capacity undergo in the neonatal period, to ascertain the main factors which influence them, and to determine, in as far as possible, how soon after birth the relations and the rate of growth in capacity which are characteristic of the suckling period are established.

Through the kindness of Dr. J. P. Sedgwick, chief of the department of pediatrics, we have had access to the records of the Pediatric Section of the Elliot Memorial Hospital of the University of Minnesota. From these we have taken the records of the amount of individual feedings, as determined by weighing before and after nursing, of 323 children during the first ten days of life. In all we secured 14,571 individual records of physiologic gastric capacity as determined by this method. The distribution of these records according to days and to the birth weights of the individuals observed is shown in Table 1. To avoid confusion we have not included a statement of the number of cases in later tables but this record can be ascertained in all cases by reference to Table 1.

Our study was limited to children having a birth weight of 2,000 gm. or over, and no twins were included in the group. Otherwise the cases were taken seriatim from the hospital records. In this group there were 187 males and 136 females. The average weight at birth of the males was 3,349 gm. and of the females 3,254 gm. These figures are somewhat below the averages determined by Taylor [12] in his study of the new-born of this same clinic, but this discrepancy is probably due to the fact that Taylor, desiring to establish a norm for full term children, excluded, as far as possible, all prematures.

10. Alliot, L.: La capacité stomicale du nouveau-nè, Thèse, Paris, 1905.

11. Scammon, R. E.: Some Graphs and Tables Illustrating the Growth of the Human Stomach, Am. J. Dis. Child. **17**:395 (May) 1919.

12. Taylor, R.: The Measurements of 250 Full-Term, New-Born Children, Am. J. Dis. Child. **17**:353 (April) 1919.

The average weight of the new-born in this same clinic as determined by Ramsey and Ally,[13] studying 300 cases, was 3,391 gm. for males and 3,276 gm. for females.

The children were breast fed five times per day, but many babies did not secure their full quota of feedings on the first day as is indicated by the small totals both of cases and feedings in column 2 of Table 1. After the first day the number of missed feedings was negligible.

TABLE 1.—MATERIAL USED IN THE STUDY OF PHYSIOLOGIC GASTRIC CAPACITY *

Age in Days	Number of Cases and Number of Feedings					
	Group I 2,000 to 2,500 Gm. Birth-Weight (Aver. 2,200 Gm.)	Group II 2,500 to 3,000 Gm. Birth-Weight (Aver. 2,840 Gm.)	Group III 3,000 to 3,500 Gm. Birth-Weight (Aver. 3,246 Gm.)	Group IV 3,500 to 4,000 Gm. Birth-Weight (Aver. 3,731 Gm.)	Group V 4,000 Gm. and Above Birth-Weight (Aver. 4,143 Gm.)	All Cases (Aver. 3,315 Gm.)
1	5	32	71	31	14	153
	(10)	(74)	(154)	(63)	(63)	(364)
2	14	63	143	75	28	323
	(65)	(311)	(698)	(370)	(135)	(1,579)
3	14	63	143	75	28	323
	(70)	(308)	(713)	(371)	(136)	(1,598)
4	14	63	143	75	28	323
	(70)	(313)	(713)	(374)	(139)	(1,609)
5	14	63	143	75	28	323
	(69)	(315)	(712)	(373)	(138)	(1,607)
6	14	63	143	75	28	323
	(70)	(314)	(714)	(373)	(138)	(1,609)
7	14	63	143	75	28	323
	(70)	(313)	(714)	(373)	(138)	(1,608)
8	14	63	142	74	28	321
	(70)	(315)	(710)	(370)	(140)	(1,605)
9	14	63	141	74	28	320
	(70)	(314)	(700)	(368)	(138)	(1,590)
10	14	59	135	71	28	307
	(62)	(279)	(614)	(331)	(116)	(1,402)
Total No. Feedings	(626)	(2,856)	(6,442)	(3,366)	(1,281)	(14,571)

* The upper figures represent the number of cases; the lower figures, in parentheses, indicate the number of feedings.

From these data was determined the average physiologic capacity, the average maximum physiologic capacity, the average capacity in per cent. of the body weight at birth, the average maximum capacity in per cent. of the body weight at birth, the average and average maximum capacity in first born and later children, the excess of the average maximum capacity over the average capacity, and the percentage increment of the average capacity and the average maximum capacity. These determinations were made for each day of the period under consideration, first for the entire series of cases and later for the same cases grouped into five classes according to birth weight.

13. Ramsey, W. R., and Alley, A. G.: Observations on the Nutrition and Growth of New-Born Infants. Am. J. Dis. Child. **15**:408 (June) 1918.

The average deviation and the average percentage deviation was determined for the average capacity in the group of cases having a birth weight ranging from 3,000 to 3,500 gm. The average and average maximum capacity in males and in females was also determined in this group.

Average physiologic capacity.—The average physiologic capacity, for all children having a birth weight of 2,000 gm. or over is shown in the seventh column of Table 2 and the curve labeled "B" in Figure 1 illustrates it graphically. The average physiologic capacity of such children as received feedings on the first day was 7 gm. This was almost doubled on the second day (13 gm.) and almost quadrupled on the third day (27 gm). On the fourth day the average capacity was a little more than six times that of the first day (46 gm.). After the fourth day the increase in average capacity was much less rapid, although it was still continued, and on the tenth day it was 81 gm., or about eleven and one-half times that of the first day. As these figures indicate, a curve of the average capacity in the first ten days (Curve B, Figure 1) shows two distinct segments. During the period from birth to the fifth day it rises rapidly, thereafter it is continued upward at a much less rapid rate.

TABLE 2.—AVERAGE CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE

Days	Average Physiologic Capacity (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	5	6	6	8	5	7
2	10	13	13	14	11	13
3	22	27	27	27	26	27
4	36	42	45	51	46	46
5	43	53	57	62	59	57
6	43	59	64	72	70	64
7	48	60	67	76	79	68
8	51	66	71	78	80	71
9	55	68	75	83	87	76
10	60	72	79	90	96	81

Average maximum physiologic capacity.—In this study the average maximum physiologic capacity has been determined by adding the sums of the largest meal ingested by each child of the series on a given day and dividing the result by the number of cases. This is a somewhat different measurement from that employed by Feer [14] and by Scammon,[11] who used the maximum meal of a given week as a basis for determining the average maximum. The value as determined by the above definition is shown in Table 3 and is represented graphically by curve "A" in Figure 1.

14. Feer, E.: Beobachtungen über die Nährungsmengen von Brustkindern, Jahrb. f. Kinderh. **42**:195, 1896.

Examining these figures and the graph it is seen that there is a close relationship between average and average maximum capacity. The average maximum capacity on the first day is 9 gm. This is more than doubled on the second day (22 gm.) and increases nearly fivefold on the third day (43 gm.). On the fourth day it is a little more than seven times as great as on the first day. Thereafter, as in the case of the average capacity, the gain is much slower and on the tenth day it is eleven and two-thirds times that of the first day, or 105 gm.

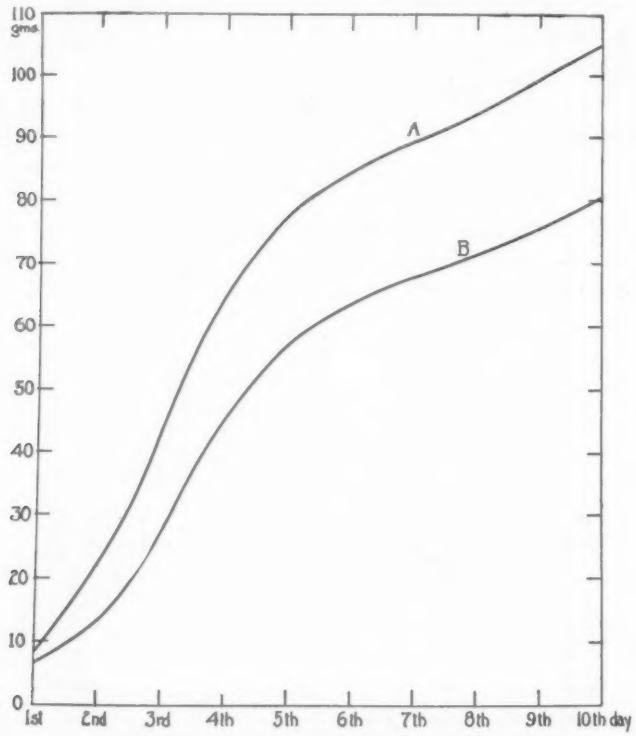

Fig. 1.—A graph showing the physiologic capacity of the stomach in the first ten days of postnatal life. A, curve of average maximum physiologic capacity; B, curve of average physiologic capacity. Based on all cases having a birth weight of 2,000 gm. or more.

The curve illustrating the changes in average maximum capacity (Curve A, Figure 1) is almost a duplicate of that of the average capacity, although all of the values are somewhat greater. It shows the same two phases as does the curve of average capacity.

Relative average and average maximum physiologic capacity.—Some interesting results are obtained if the average physiologic capacity and the average maximum capacity are calculated in terms

TABLE 3.—Average Maximum Physiologic Capacity of the Stomach in the Ten Days of Postnatal Life

Days	Average Maximum Physiologic Capacity (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	7	9	9	10	6	9
2	18	22	23	24	19	22
3	35	41	43	45	44	43
4	53	60	65	71	65	65
5	58	70	78	85	85	78
6	63	78	86	94	88	85
7	64	82	91	98	100	90
8	65	86	94	105	100	94
9	81	87	99	107	114	99
10	84	92	104	115	122	105

TABLE 4.—Average Physiologic Capacity of the Stomach in the Ten Days of Postnatal Life, Calculated in Per Cent. of the Body Weight at Birth

Days	Average Physiologic Capacity in Per Cent. of the Body-Weight at Birth					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	0.23	0.23	0.22	0.23	0.13	0.21
2	0.44	0.45	0.39	0.38	0.26	0.39
3	0.97	0.94	0.83	0.74	0.63	0.81
4	1.61	1.47	1.40	1.38	1.11	1.38
5	1.92	1.87	1.76	1.66	1.43	1.72
6	1.90	2.08	1.97	1.93	1.69	1.95
7	2.12	2.12	2.07	2.05	1.91	2.06
8	2.26	2.33	2.18	2.09	1.93	2.16
9	2.45	2.40	2.31	2.23	2.10	2.28
10	2.66	2.52	2.42	2.42	2.33	2.43

TABLE 5.—Average Maximum Physiologic Capacity of the Stomach in the First Ten Days of Postnatal Life, Calculated in Percentages of the Body Weight at Birth

Days	Per Cent. of Body-Weight					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	0.29	0.32	0.27	0.28	0.14	0.27
2	0.80	0.79	0.70	0.64	0.47	0.68
3	1.54	1.46	1.31	1.22	1.06	1.29
4	2.35	2.13	2.00	1.92	1.57	1.96
5	2.57	2.46	2.40	2.28	2.06	2.35
6	2.80	2.75	2.65	2.53	2.14	2.58
7	2.84	2.89	2.79	2.63	2.42	2.73
8	2.87	3.05	2.90	2.80	2.42	2.85
9	3.59	3.08	3.06	2.87	2.75	2.99
10	3.71	3.25	3.22	3.08	2.95	3.17

of the body weight at birth. These figures are shown in Tables 4 and 5 and the curves shown in Figure 2 are their graphic expression. The average gastric capacity in the first day is equal to about one-fifth of one per cent. of the body weight. By the second day this has risen to about 0.8 per cent. and on the fourth day to nearly 1.4 per cent. of the birth weight. After the fourth day the relative gastric capacity, like the actual average capacity, increases more slowly. By the tenth day the average capacity is equal to about 2.4 per cent.

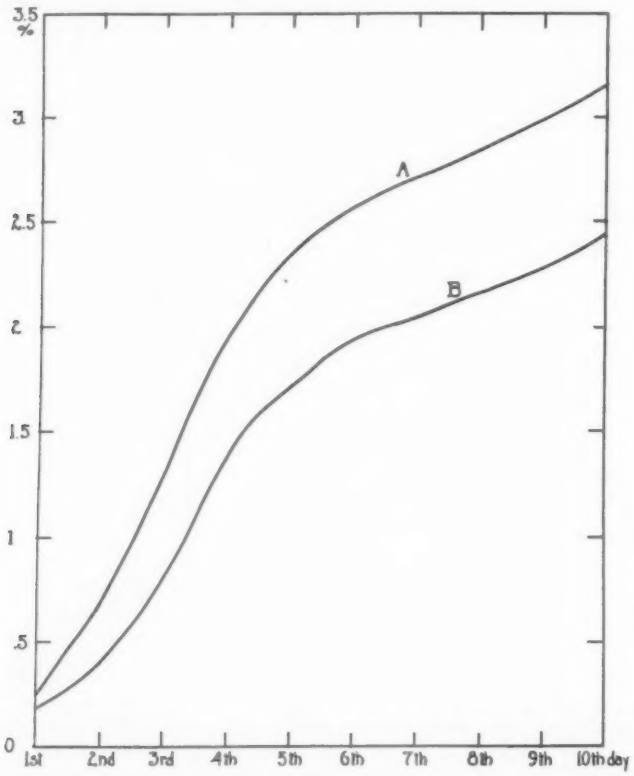

Fig. 2.—A graph showing the physiologic capacity of the stomach in the first ten days of postnatal life, as determined in per cent. of the body weight at birth. A, relative average maximum physiologic capacity; B, relative average physiologic capacity. Based on all cases having a birth weight of 2,000 gm. or more.

of the body weight at birth or about twelve times more than the average capacity on the first day.

The changes in the relative average maximum capacity are very similar to those in the relative average capacity. Starting at 0.27 per cent. on the first day, the relative average maximum rises rapidly

to nearly 2 per cent. by the fourth day. Thereafter the amount increases much more slowly up to the tenth day, when it stands at nearly 3.2 per cent.

The curves based on these figures are much alike and are quite similar to those of the average and the average maximum capacity. They show the same characteristics of the rapid initial rise until the fourth day and the slower elevation from that point to the end of the period of observation (Fig. 2).

Relation between body weight and physiologic capacity.—The results which have been presented are based upon the study of the

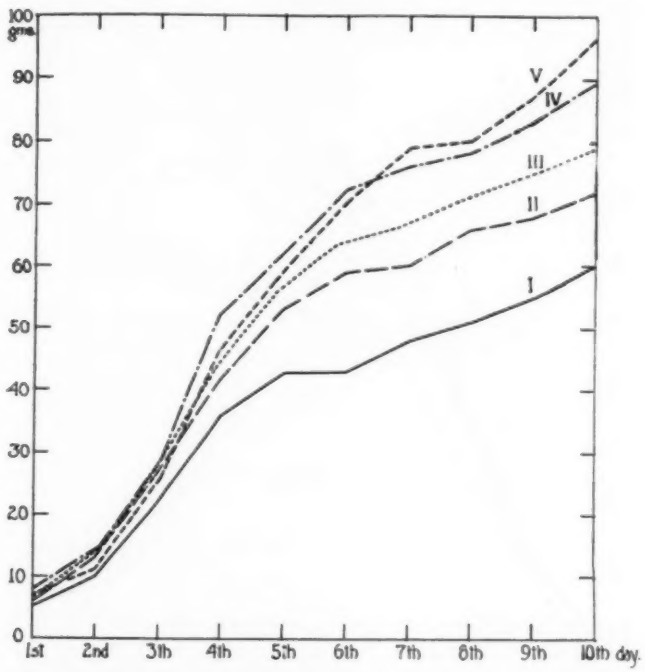

Fig. 3.—Average physiologic gastric capacity in the first ten days of postnatal life, in groups of children arranged according to birth weight. Curve I, average capacity of children with a birth weight of from 2,000 to 2,500 gm. Curve II, average capacity of children with a birth weight of from 2,500 to 3,000 gm. Curve III, average capacity of children with a birth weight of from 3,000 to 3,500 gm. Curve IV, average capacity of children with a birth weight of from 3,500 to 4,000 gm. Curve V, average capacity of children with a birth weight of 4,000 gm. or more.

entire series of cases having a body weight of 2,000 gm. or over. The same data were studied further by arranging the cases into groups according to body weight at birth. Five of these groups were established: Group I, from 2,000 to 2,500 gm.; Group II, from 2,500 to 3,000 gm.; Group III, from 3,000 to 3,500 gm.; Group IV, from 3,500

to 4,000 gm. and group V, 4,000 gm. and over. The results obtained by this procedure are shown in Tables 2, 3, 4 and 5, and by the curves shown in Figures 3, 4, 5 and 6.

The absolute average gastric capacity evidently increases with the body weight in Groups I, II, III and IV (children weighing between 2,000 and 4,000 gm.). As will be seen in Table 2 and in Figure 3,

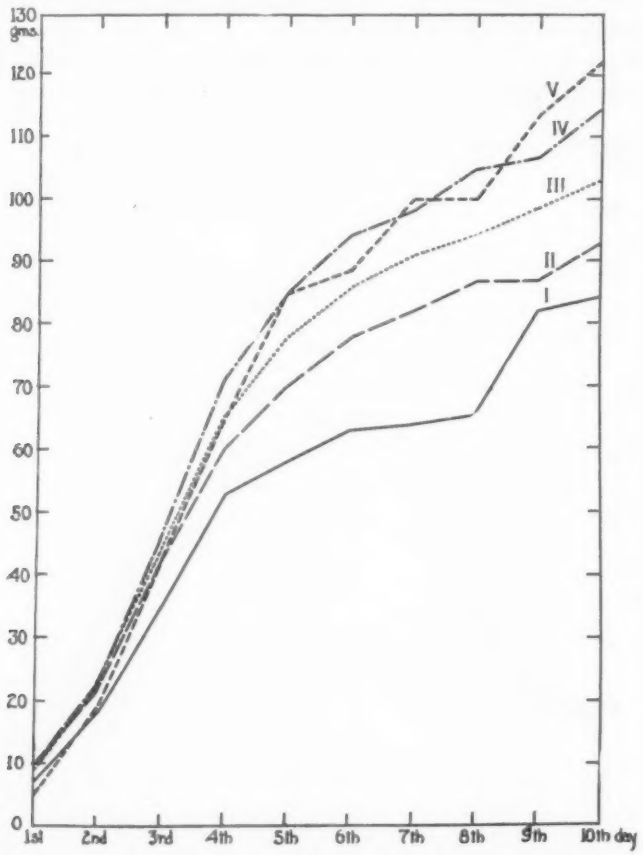

Fig. 4.—Average maximum physiologic gastric capacity in the first ten days of postnatal life, in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000 gm. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of from 4,000 gm. or more.

there is a slight difference in favor of the groups of heavier children even on the first day and this becomes more noticeable in the latter part of the period. Group V (children having a birth weight of 4,000 gm. or over) shows a somewhat different condition. During the

first three days of postnatal life the average capacity in these infants is slightly below that of the other groups of children and is only a little more than that of Group I (weighing from 2,000 to 2,500 gm.). However, the capacity of the heaviest group rises rapidly on the fourth and fifth days and on the sixth day and thereafter it exceeds that of any of the other groups.

The absolute average maximum capacity shows relations similar to those just described. It rises with the birth weight in all groups under 4,000 gm., but Group V (of 4,000 gm. and over) shows the

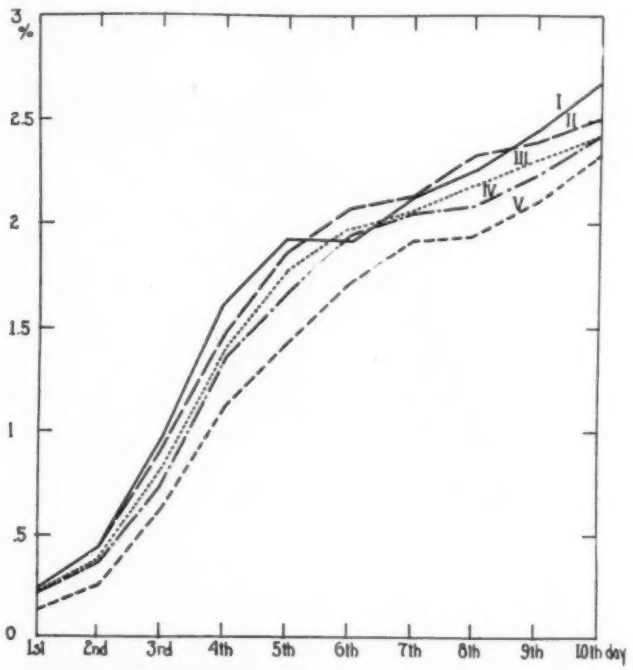

Fig. 5.—A graph illustrating the relative average physiologic gastric capacity in the first ten days of postnatal life in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of 4,000 gm. or over.

lowest average maximum capacity on the first day. It is not until the ninth day that this value is greater in the heaviest than in the lighter groups of children.

The figures on the *relative* physiologic capacity, i. e., the capacity as calculated in per cent. of the birth weight, show relations which are quite different from those of absolute physiologic capacity.

On the first day the relative average capacity is approximately the same in all groups of children having a birth weight under 4,000 gm. Thereafter, with one minor exception, the relative capacity is always greater in the lighter than the heavier groups. This difference, although not very great, is practically always present. The children

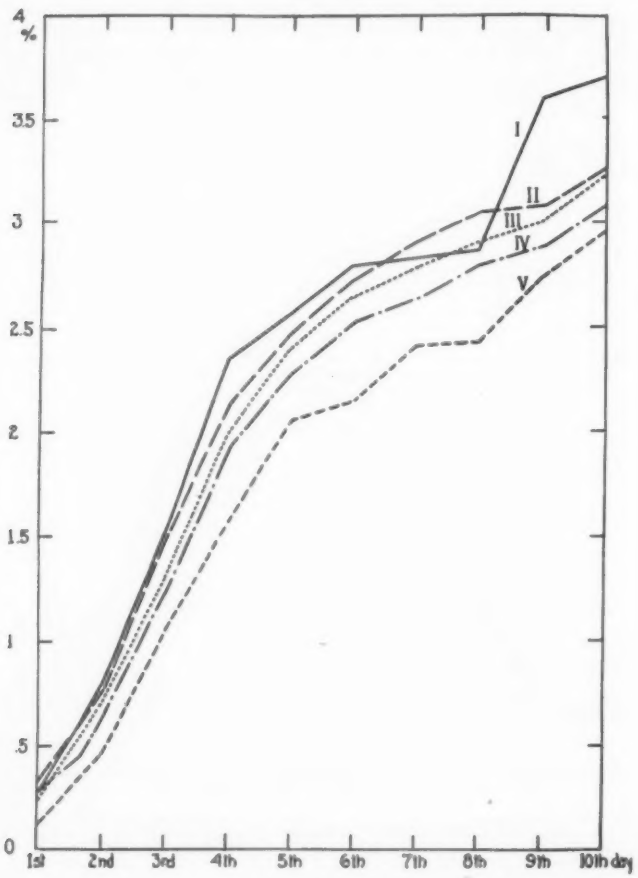

Fig. 6.—A graph illustrating the relative average maximum physiologic gastric capacity in the first ten days of postnatal life in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000 gm. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of 4,000 gm. or over.

of Group V (of 4,000 gm. and over) have a relative capacity only a little over one-half as great as that of the lighter groups and the average value always remains far below that of the other groups during the period of observation (Fig. 5).

The history of the relative maximum capacity is similar to that of the relative average capacity. The general rule that the smaller the birth weight of the group the larger the relative capacity holds true throughout except for the first day, when the relative maximum capacity is about the same in all groups of children under 4,000 gm. in weight, and for the eighth day, when this value in Group I (from 2,000 to 2,500 gm. in weight) falls below that of Group II (from 2,500 to 3,000 gm. in birth weight).

It may, therefore, be concluded that while the heavier children of this series tend to have a larger absolute physiologic capacity than do the lighter ones, this capacity does not increase directly in proportion with body size.

TABLE 6.—Differences in the Average Physiologic Gastric Capacities of First-Born and Later Children *

Days	Differences in Capacities (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	+1	−1	+1	+6	+6	0
2	0	+6	−3	+4	+7	+2
3	0	+9	−5	+4	+15	+3
4	0	+6	+1	+12	+23	+5
5	−4	+3	−4	+3	+6	−1
6	+7	−1	−10	−2	+17	−1
7	+5	−4	−13	+2	+20	0
8	+8	−3	−8	+3	+19	0
9	−2	−2	−5	+2	+34	+3
10	−13	+4	−3	0	+18	+3

* Figures preceded by a minus sign indicate a greater average capacity in first born children. Figures preceded by a plus mark indicate a greater average capacity in later children.

Physiologic capacity in first-born and later children.—The average and the relative average physiologic capacity were calculated separately for first-born and for later children. This was done first for the entire series of cases and then for the several groups arranged according to birth weight. The differences between the first born and later children were then determined from these figures and are shown in Table 6. The figures in this table which are preceded by a plus sign indicate an excess in capacity of the later children over the first born, and those preceded by a minus, an excess in capacity of the first born over the later born. If Groups I to IV, inclusive, of this table are examined, it will be seen that there are no consistent differences in these values in the two classes of children. However, in Group V, having a birth weight of 4,000 gm. or over, the capacities of later children are consistently and considerably greater than those of first born infants. As the relative average capacities showed practically identical results they will not be considered here in detail.

Physiologic capacity in males and females.—The average and the average maximum capacities were determined separately for males and for females in Group III (children having a birth weight of from 3,000 to 3,500 gm.). No consistent sex difference in capacity, as determined by either of these measures, was observed.

Variability in average physiologic capacity in the neonatal period.—It is, of course, well known that the variation in the amounts ingested at single meals by young infants is very great, but apparently no attempt has been made to measure it. In order to secure some measure of this value we determined the range of variation and the average deviation and the percentage deviation in the feeding records of the group of children having a birth weight ranging from 3,000 to 3,500 gm. (Group III).

The range of variation is easily secured by determining the maximum and minimum meal of the entire series of feeding records for each day of the period of observation. This determination, while of interest, tells us little of the actual amount of variation in our material, which is much better indicated by the average deviation and the percentage deviation. The average deviation is calculated by first determining the amount that each observation differs from the average of the whole series. These amounts are then added (plus and minus signs being disregarded) and the sum is divided by the total number of cases. The result expresses the average deviation (in this case in grams). This value can be readily converted into a per cent. of the average capacity by dividing by the average of all cases and multiplying by 100.

TABLE 7.—VARIABILITY IN AVERAGE PHYSIOLOGIC GASTRIC CAPACITY IN IN THE FIRST TEN DAYS OF POSTNATAL LIFE *

Days	Number of Observations	Average Capacity, Gm.	Minimum Feeding, Gm.	Maximum Feeding, Gm.	Average Deviation, Gm.	Per Cent. Deviation
1	154	6	2	60	3.6	60.0
2	698	13	4	80	6.8	52.3
3	713	27	3	110	15.2	56.3
4	713	45	5	130	17.9	39.8
5	712	57	8	140	19.2	34.7
6	714	64	2	165	19.3	30.1
7	714	67	10	145	20.6	30.7
8	710	71	10	160	21.3	30.0
9	700	75	5	148	20.5	27.3
10	614	79	10	210	20.6	26.0

* Based upon the feeding records of children with a birth-weight ranging from 3,000 to 3,500 grams.

The results of these calculations are shown in Table 7 and are, in part, graphically expressed in Figure 7. The minimum meal during the first ten days ranges from 2 to 10 gm. and shows no particular regularity. The maximum meal was 60 gm. on the first day and rises

fairly steadily to 160 gm. on the sixth day. Thereafter it is quite irregular. The average deviation rises rapidly in the first three or four days, but after the fourth day it stands between 19.2 and 21.3 gm., which is surprisingly constant considering the nature of the material. The percentage deviation in the first three days of postnatal life forms over one-half of the average capacity. It then decreases, at first rapidly and later quite slowly, during the remainder of the period. In round numbers the percentage variability in the

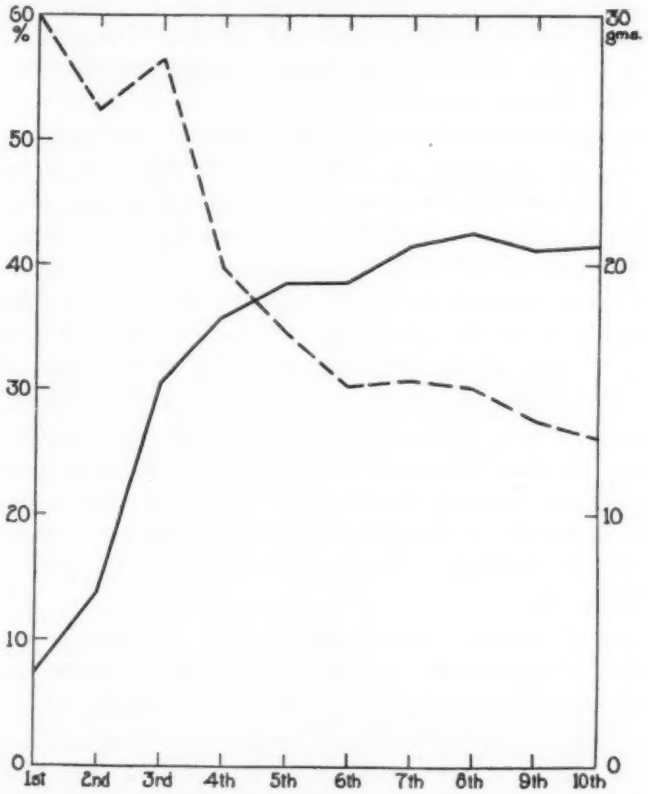

Fig. 7.—A graph illustrating the changes in variability in average physiologic gastric capacity in the first ten days of postnatal life. Curve A (in solid line), average deviation in average physiologic capacity. Curve B (in broken line), percentage deviation in average physiologic capacity. Based on the feeding records of a group of 143 children having a birth weight ranging from 3,000 to 3,500 gm.

first third of the period of observation is twice as great as in the last third.

This variability seems to have no close relation to the feeding schedule of the children. The maximum meal of the day may occur at any of the five feeding periods. In the first four days it is less

frequently the first meal in the morning, while in the last six days the last meal in the evening is less often the largest one of the day. However, the differences in distribution of the maximum meal among the several feeding periods in the entire group of cases are so slight that no definite conclusion can be drawn from them.

In our entire series of cases there were forty-six instances in which a meal was missed. In eighteen cases the succeeding meal was smaller than the average; in twenty-two cases it was larger than the average, and in six cases it was the same as the average meal. The small amount of data which we have on this subject does not indicate that loss of a meal is compensated for by a larger succeeding one, in the first few days of postnatal life.

Percentage increment in physiologic capacity in the neonatal period.—The measures of growth in gastric capacity which have been described in the preceding sections of this paper are mainly in the form of absolute quantities. A much more striking exposition of the changes is given by the daily percentage increment. This value is calculated by determining the gain in capacity for each day in per cent. of the capacity of the day preceding. The results of these calculations are shown in graphic form in curves B and C in Figure 8. The increment in average physiologic capacity is over 80 per cent. on the second day and over 100 per cent. on the third day. Thereafter, it falls rapidly to about 20 per cent. on the fourth day and to less than 10 per cent. for the last third of the period of observation. The percentage increment in maximum physiologic capacity follows much the same history although it is greater at the beginning of the period (Curve B, Fig. 8).

Relation of average physiologic capacity to average maximum physiologic capacity in the neonatal period.—In a recent paper one of us pointed out that the average maximum physiologic capacity, from the third week after birth until the seventh month, is about one-half greater than the average physiologic capacity. The relation of these two values in the period of the new-born shows several striking changes. On the second day the average maximum capacity is about 25 per cent. greater than the average capacity. On the second day it is 70 per cent. greater. It then drops until the fifth or sixth day to about one-third more than the average capacity (Curve A, Fig. 8.).

The anatomic capacity of the stomach in the new-born and the neonatal period.—The anatomic capacity of the stomach in the new-born, as determined by a number of observers using a variety of methods, falls between 25 and 35 c.c. Most of the published work on anatomic capacity at birth does not include records of the individual

cases and therefore is not very satisfactory. The most complete published data on this subject are those of Alliot,[10] and to these we have been able to add a small number of personal observations. The combined data available to us are shown in Table 8. The average anatomic capacity in a series of 25 new-born children ranging in birth weight from 2,000 to 4,300 gm. was 33 cc. In thirteen premature children having a birth weight ranging from 1,200 to 2,000 gm. the average

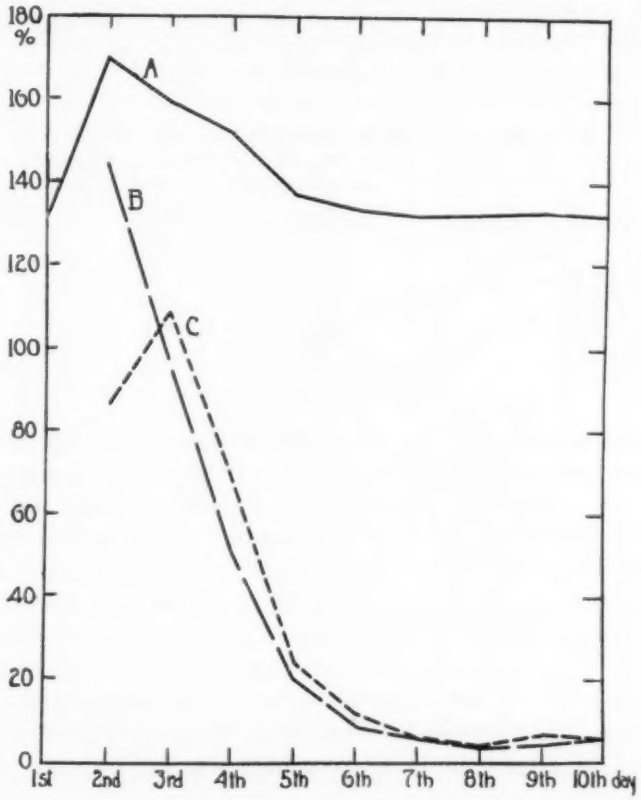

Fig. 8.—Curve A, percentage which the average maximum physiologic capacity forms of the average physiologic capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over. Curve B, percentage increment in the average physiologic gastric capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over. Curve C, percentage increment in the average maximum physiologic gastric capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over.

capacity was 22 c.c. In new-born children having a body weight between 2,000 and 3,000 gm. the average capacity was 30 c.c.; and in those between 3,000 and 4,000 gm. body weight, 35 c.c. Three very large infants, having a body weight of 4,000 gm. or more, had an

average capacity of 38 c.c. Thus the anatomic capacity at birth appears to increase somewhat with the body weight as does the physiologic capacity of the neonatal period.

The relative anatomic capacity, i. e., the capacity of the stomach calculated in per cent. of the body weight (c.c. considered equivalent to gm.), was, for this same series of cases, 1.3 per cent. in infants having a body weight below 2,500 gm,, 1.1 per cent. in children weighing between 2,500 and 3,500 gm., and 0.9 per cent. in children weighing 3,500 gm. or more. Thus the relative anatomic capacity of the stomach decreases as the body weight increases, as does the relative physiologic capacity in the neonatal period.

TABLE 8.—AVERAGE ANATOMIC CAPACITY OF THE STOMACH IN THE NEW-BORN AS DETERMINED BY ZUCARRELLI'S METHOD

Range of Body-Weight, Gm.	Average Body-Weight, Gm.	Number of Cases	Average Anatomic Capacity, C.c.
1,500 to 2,000	1,710	13	22
2,000 to 2,500	2,140	3	30
2,500 to 3,000	2,740	7	30
3,000 to 3,500	3,210	6	35
3,500 to 4,000	3,710	6	35
4,000 or more	4,340	3	38
2,000 or more	3,140	25	33

Detailed observations on the anatomic capacity of the stomach in the period between birth and the end of the second postnatal week are not very numerous. The average anatomic capacity of the first week, as indicated by the data of Fleishmann,[15] Froloffski,[16] Stössl,[17] Zuccarelli [18] and Rotch,[19] is approximately 45 c.c. or nearly one-third more than the capacity at birth. In the second week the data collected by these same observers and by Holt,[20] d'Astros,[21] Politzer,[22] Muggia [23] and others, indicate that the anatomic capacity is about 75 c.c. These figures are based on determinations by a variety of methods, although the majority of observations were made with Zuccharelli's method. The curve of growth in anatomic capacity in the neonatal period is

15. Fleischmann: Klinik der Pädiatrik, Wien., 1875.
16. Froloffski: Material on the Anatomy of the Digestive Tract in Sucklings, Diss., St. Petersburg, 1876.
17. Stössl: Semiotik des Kindesalters, 1875.
18. Zuccarelli, P.: L'estomac de l'enfant, Thèse, Paris, 1894.
19. Rotch, T. M.: Pediatrics, Ed. 1, Philadelphia, 1896, p. 76 et seq.
20. Holt, L. E.: Observations on the Capacity of the Stomach in Infancy, Arch. Pediat. **7**:960, 1891.
21. d'Astros: L'estomac de l'enfant; sa dilatation, Rev. de Mal. de l'enf. 12, 1894.
22. Pollitzer: Ideen zur Behandlung einer wissenschaftlichen Diatetik, Jahrb. f. Kinderh. 4, 1858.
23. Muggia, A.: La capacité e la posizione del ventricalo nei bambini, Giorn d. r. Accad. di med. di Torino, Series 4 **2**:351, 1896.

shown in semidiagrammatic form in Figure 9. As will be seen from this figure, the anatomic capacity of the stomach appears to increase at a uniform rate throughout the period and there are no indications of two distinct phases of growth comparable with those seen in all of the graphs of physiologic capacity.

Although the growth of the anatomic capacity of the stomach in the neonatal period appears to be quite slow if compared with the growth in physiologic capacity, it is very rapid compared with the growth in fetal life. In the first week after birth the anatomic capacity increases more than it does in the entire last third of fetal life, and the absolute increase in the first two weeks of postnatal life is considerably greater than the entire prenatal growth.

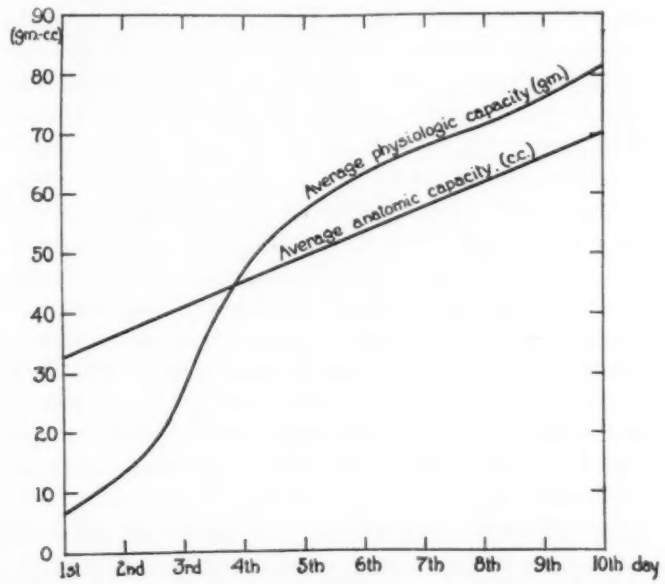

Fig. 9.—Semidiagrammatic curves illustrating the relation between the average physiologic capacity and the average anatomic capacity of the stomach in the first ten days of postnatal life.

DISCUSSION

The discussion of our data will be limited to a comparison of anatomic and physiologic capacity in the neonatal period and to a consideration of certain peculiarities of physiologic capacity during this time.

It has been pointed out by one of us (Scammon [11]) that during the greater part of the suckling period there is a close correlation between the anatomic capacity of the stomach, as determined post-mortem, and the average physiologic capacity, as determined by weigh-

ing before and after feeding. The physiologic capacity, as determined by this method, was found to be approximately equal to the anatomic capacity of the organ under a pressure of between 15 and 20 centimeters of water. It was also noted that practically all of the technics used in determining anatomic capacity distend the viscus to about the same extent as does a pressure of 15 centimeters of water.

The relation between anatomic and physiologic capacity in the neonatal period is somewhat more complex than in the suckling period proper. It is represented in a semidiagrammatic fashion by the two curves shown in Figure 9. At birth the anatomic capacity of the stomach is roughly four and one-half times the physiologic capacity (on the average as 33 to 7). During the first half of the first week of postnatal life the anatomic capacity increases about one-third, while the physiologic capacity is increased about six-fold. The curves of these two measures of gastric capacity therefore converge and meet between the third and fourth day. Thereafter the anatomic capacity continues to increase at about the previous absolute rate. The physiologic capacity, however, rises much more slowly and is soon established slightly above that of the anatomic capacity. Evidently the constant relation which exists between the average physiologic and the average gastric capacity during the greater part of the suckling period is established during the middle part of the first week.

Taken as a whole, the figures on physiologic capacity which are presented here are distinctly higher than those of the earlier investigators mentioned at the beginning of this paper. This is not surprising considering that most of these workers made their observations upon infants which were fed eight or more times a day. The differences between our results and those of other recent observers are not very great.

The most noticeable feature of this series of observations is the marked change in physiologic capacity which takes place on the fourth or fifth day. This change is seen in all of the values of physiologic capacity which we have determined—in the absolute physiologic capacity both average and average maximum, in relative capacity, in percentage increments of both the average and the average maximum capacity, and in the two simple measures of variability which we have employed. In the first four days all measures of gastric capacity show a very rapid increase while in the last six days of the period of observation the increment is comparatively slow. In the first four days, also, the degree of variability in physiologic capacity is changing rapidly while in the latter part of the period it stands at a fairly constant figure.

The rapid gain in physiologic capacity of the first four days is probably no index of the actual growth of the stomach of this period

since it is almost the end of this time before the physiologic capacity of the stomach equals the anatomic capacity. The figures and curves relating to this part of the period of observation are criteria of the ability of the mother to furnish food and of the ability of the infant to ingest it rather than actual measures of the growth of the stomach in cubic capacity. Similarly, the indices of variability which have been presented are measures of the variability of the above factors rather than of gastric capacity proper.

The later gain in physiologic capacity, from the fourth to the eleventh day, probably approaches much closer to the real index of the stomach's growth since it is substantially the same as the increase in anatomic capacity.

Unfortunately, we have no available data on the weight or surface area of the stomach in the first few days after birth to enable us to determine whether the growth of the organ in these respects is comparable with the changes in capacity. It is known, however, that the growth of the stomach in net weight is very great in the first postnatal months when the organ is increasing most rapidly in capacity.

As has been pointed out, our figures indicate that the absolute physiologic capacity increases, though not directly, with the birth weight of the child. This finding agrees with the earlier observations of Ssnitkin [5] on physiologic capacity. On the other hand, Holt [20] in his study of anatomic capacity, found no relation between this measure and body weight. However, his observations were made mainly on older children. That the relative physiologic capacity of groups of lighter children is greater than that of heavier groups has not, we think, been specifically pointed out previously, although several recent studies, such as those of Reicke [24] and Hammett,[25] have noted a relatively rapid rate of growth of premature infants which might be expected to be associated with a greater relative food intake. There are few published figures on the relative gastric capacity in the neonatal period. The only ones based on an extensive series of cases are those of Ssnitkin,[5] who calculated that the average meal was equal to 1 per cent. of the body weight plus 1 gm. for each day of postnatal life. This rule gives values far below those quoted in our tables despite the fact that our percentages are figured on the birth weight rather than the actual weight at the time of feeding. This discrepancy is probably due in part to the feeding methods employed in Ssnitkin's cases, and in part to the fact that his observations extended over the entire first month while ours were limited to the first ten days of postnatal life.

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24. Reicke, A.: Das Wachtum der Frühgeburten in den ersten Lebensmonaten, Ztschr. f. Kinderh. **13**:332, 1915.

25. Hammett, F. S.: The Relation Between Growth Capacity and Weight at Birth, Am. J. Physiol. **45**:396, 1918.

Our figures show no constant differences in the physiologic capacity of first born and later children, except for the group of heaviest cases. This result was unexpected for a priori one might expect that first born children would take smaller meals than later ones both because of greater birth trauma, which would limit their power of nursing, and because the mammary glands of primiparae begin to function a little later after delivery than do those of multiparae. While the difference in this later factor in multiparae and primiparae is one of hours only, according to Landois'[9] observations, still one might expect it to affect our averages slightly. It may be that our findings in this particular are due to the nature of the material studied, for it is the practice of the University Hospital to receive all primiparae for delivery while multiparae are only received when there is record of previous difficult deliveries, when pathologic symptoms are observed, or when the social conditions of the mother are adverse. By far the larger number of multiparous mothers of our series were admitted to the hospital for delivery because of adverse social circumstances. Possibly these circumstances have influenced the physical condition of the mothers to the extent of limiting the milk supply during the first ten days postpartum.

The group of heaviest children in our series (those having a birth weight of 4,000 gm. or more) show several peculiarities of gastric capacity not seen in the groups of smaller infants. These heavier children have smaller relative anatomic capacities at birth than do the lighter ones and their physiologic capacities, both absolute and relative, are smaller in the first week of life. In the early part of the second week the absolute physiologic capacity in this group rises above that of the lighter groups of children but the relative physiologic capacity remains far below throughout the period of observation. In this group, also, parity has a distinct effect on physiologic capacity, and the averages of first born children are distinctly below those of later children. We are inclined to attribute most of these peculiarities in physiologic capacity to the greater trauma which these children undergo at birth.

SUMMARY

The results of this study may be summarized as follows:

1. The average physiologic capacity of the stomach in the first day after birth is about 7 gm. This practically doubles in the second day, quadruples on the third, and increases almost sevenfold on the fourth. After the fourth day, the increase is much slower and the average capacity on the tenth day is 81 gm. or over eleven times that of the first day. The average maximum physiologic capacity increases in much the same manner as the average physiologic capacity.

It is about one-fourth greater than the average physiologic capacity on the first day and about two-thirds greater on the second. Thereafter the difference between the two measures decreases rapidly until the sixth day. After the sixth day the average maximum capacity remains about one-third more than the average capacity.

2. The relative physiologic capacity increases in much the same way as the absolute physiologic capacity. It is equal to 0.21 per cent. of the birth weight of the body on the first day, to 1.38 per cent. on the fourth day, and 2.43 per cent. on the tenth day. The relative maximum capacity is equal to 0.27 per cent. of the initial body weight on the first day, to 1.96 per cent. on the fourth day, and to 3.17 per cent. on the tenth day.

3. In the first ten days parity has no constant effect on the physiologic capacities of children having an initial body weight of from 2,000 to 4,000 gm. Sex has no effect on the physiologic capacity in this period.

4. The average deviation in physiologic capacity rises rapidly from the first to the fourth day. Thereafter it increases very slowly. The percentage deviation decreases rapidly until the fifth day and thereafter continues to drop very slowly.

5. All indices of physiologic capacity indicate that there is a distinct change in the nature of this value about the fourth day. Until this time the increase in capacity, in whatever manner it is calculated, is very rapid, thereafter it is much slower. In the first four days average deviation in capacity is increasing rapidly and percentage deviation is decreasing rapidly. After this time both of these measures change very little.

6. The anatomic capacity of the stomach at birth averages 33 c.c. This is increased about one-third in the first three or four days and is a little more than doubled in the second week. There is no indication of two definite stages in the development of anatomic capacity in the neonatal period corresponding to the two phases of physiologic capacity. Anatomic capacity and physiologic capacity approximate one another about the fourth day. Thereafter physiologic capacity runs parallel to the anatomic capacity but is slightly greater. This agrees with previous findings regarding this relation throughout the greater part of the suckling period.

7. The curve representing average physiologic capacity in the first ten days of post natal life shows two phases. The first segment, extending from birth to the fourth day, shows little relation to the actual capacity of the organ but is rather a measure of the ability of the average mother to furnish nourishment in this period and the ability of the average child to receive it. The second segment, extend-

ing from the fourth to the tenth day, is probably a fair measure of the actual increase in gastric capacity comparable with similar measures of this value made at later times in the sucking period.

8. The gastric capacities of children weighing 4,000 gm. or over at birth are somewhat different from those of infants of lighter weights. Both the average and the average maximum physiologic capacities of this group are smaller than those of lighter children in the first three or four days of post natal life but these values increase rapidly in the fifth and sixth days and before the end of the period exceed those of smaller infants. Parity has a slight but distinct effect on physiologic capacity in this group of large infants, and first born children have a smaller capacity than do the later born. The anatomic capacities of children of this group are somewhat greater absolutely but smaller relatively than in children of the lighter groups.

STUDIES IN SPASMOPHILIA

II. ELECTRICAL REACTIONS OF OLDER CHILDREN

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In the first paper of this series [1] I stated that the term spasmophilia was being used to denote that latent condition in infants one year old or less in which a heightened electrical irritability is shown by an anodal opening contraction (A O C) of less than 5 ma. and requiring less current than the anodal closing contraction (A C C), a phenomenon which Thiemich was the first to consider as spasmophilic; or a cathodal opening contraction (C O C) with less than 5 ma., known as Escherich's sign. It was further stated that for the active condition manifesting convulsions, laryngospasm, carpopedal spasm and other forms of spasm the term tetany is reserved. This classification is recommended by others, notably Langstein and Meyer.

In testing the electrical reactions of older children, one is confronted with the question: Do the same standards of electrical diagnosis for infants apply to children more than 2 years of age?

Combing an abundant literature on tetany and spasmophilia one encounters few attempts to answer this question. In 1886, Stinzig [2] established the normal value for the C C C in adults but went no farther. Von Pirquet's standards are based on a study of twenty-four children under 2 years of age and fulfill the requirement for spasmophilia if A O C is less than 5 ma. Sedgwick [3] in 1912, reported some electrical reactions on mothers of infants with tetany, and cites an A O C = 4.6 (in the mother) and greater than the A C C as "slightly spasmophilic." Two years later the same observer [4] applies electrical tests to the parents and grandparents of spasmophilic infants. Wilcox [5] in a study of infantile tetany states that "it is very difficult to define exactly the normal electrical response of childhood." His observations are on infants under 2 years of age.

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1. Von Meysenbug, L.: Studies in Spasmophilia. I. Spasmophilia and Vitamins, Am. J. Dis. Child. **20**:206 (Sept.) 1920.
2. Stinzig: Ueber Electrodiagnostische Grenzwerte, Deutsch. Arch. f. klin. Med. **39**:76, 1886.
3. Sedgwick, J. P.: Spasmophilia in Children with Illustrative Cases, St. Paul M. J., October, 1912.
4. Sedgwick, J. P.: Spasmophilia with Especial Reference to Familial Reactions and Repeated Absences, Am. J. Dis. Child. **7**:140 (Feb.) 1914.
5. Wilcox, H. B.: The Diagnosis of Infantile Tetany, Am. J. Dis. Child **1**:393 (June) 1911.

It was apparently assumed up to this time that the electrical standards for infants were applicable to older children and adults in the diagnosis of spasmophilia. In a study of older children, Holmes,[6] in 1916, added valuable information to the subject. He tested the electrical reactions of 400 tetany-free children ranging in ages from one month to 13 years, and gives in tabular form the average values for the different ages. The average values are condensed in Table 1.

TABLE 1.—ELECTRICAL REACTIONS OF TETANY-FREE CHILDREN

Ages	No. Examined	C C C	A C C	A O C	C O C
1- 5 years	105	2.9	4.2	4.3	>5
5-13 years	172	1.7	3.7	3.1	>5

In the first group A O C > A C C.

A very striking change is the sudden lowering of the values after the fifth year, especially the A O C, which now becomes less than A C C. Chvostek's sign was obtained in only one of 228 children up to the fifth year. Coincident with the lowered electrical values after this age the Chvostek increases in frequency up to 25 per cent. of all children at 9 years.

Holmes finds difficulty in interpreting some of the low values found in apparently normal children. Reviewing his work, several points need emphasis: The children examined were not normal healthy children, as all were hospital patients, coming for relief of some ailment. May not some of their symptoms have been milder and obscure manifestations of spasmophilia, such as enuresis, petit mal, mild gastrointestinal disturbances, vasomotor instability; such symptoms as constitute, according to many observers, spasmophilic diathesis? No mention is made of such symptoms existing, nor is evidence presented that their possible existence was investigated.

The study was carried on in the winter and early spring when tetany is prevalent and spasmophilia is about to become manifest. A similar study in July and August would be interesting, for there is good reason for the belief that the high percentage of Thiemich's signs that Holmes found would be lower. I shall touch on this point again.

Do such anodal reactions designate a neuropathic or spasmophilic constitution? It would be drastic to condemn as neuropaths or spasmophilics 75 per cent. of children from 6 to 7 years old. And yet these anodal reactions contrast so sharply with the reactions obtained

6. Holmes, J. B.: Reliability of Electrical Diagnosis of Tetany with Especial Consideration of the Electrical Values Found in Normal Children, Am. J. Dis. Child. **12**:1 (July) 1916.

in the other 25 per cent. at this age, where frequently only C C C is less than 5 ma., that it is difficult to let the lower values go unchallenged.

The most recent study of spasmophilia in older children reported is that of Stheeman.[7] This observer regards Thiemich's and Escherich's signs as pathognomonic of spasmophilia. Chvostek's sign denotes first degree spasmophilia; Erb's sign denotes second degree; and the presence of both is indicative of advanced types. Of 100 children examined, Stheeman found sixty-three with "spasmophilic stigmata." The Chvostek and Erb signs occurred together in thirty-two; fourteen children had only the Erb sign and seventeen had only the Chvostek sign. The age distribution of these groups is shown in Table 2. These figures, he claims, show the frequency of the spasmophilic syndrome without tetany.

TABLE 2.—INCIDENCE OF ERB AND CHVOSTEK SIGNS

Age	Erb and Chvostek		Erb only		Chvostek only	
0- 3 years	9	28%	2	14%	7	44%
4- 7 years	9	28%	4	28%	8	47%
7-12 years	14	44%	8	64%	2	12%
	32		14		17	

As constitutional spasmophilic anomalies Stheeman finds: (1) digestive disturbances, deficient nutrition and other dystrophies; (2) irritability and weakness of (a) vasomotor system (angiospasm, spastic anemia etc.); (b) vegetative nervous system (vagotonia, cramps, hypermotility, atony, spastic obstipation, enuresis); (c) upper neurons (psychasthenia, neurasthenia). He found that 72 per cent. of the thirty-two children having both Erb and Chvostek's signs had digestive disturbances, and 90 per cent. had irritability and weakness of the vasomotor system. To support his contention that the electrical reactions which he designates as spasmophilic are really so, he endeavored to determine the blood calcium by means of Wright's method. This method, now obsolete, consists in drawing fresh blood into capillary tubes which contain varying strengths of an ammonium oxalate solution from fortieth to hundredth normal. The calcium is thus precipitated, and its concentration is assumed to be in direct ratio to the amount of oxalate required to prevent clotting. The method is, of course, fallacious in that it assumes calcium to be the only factor concerned in blood clotting. Normally fortieth, fiftieth and sixtieth normal solutions will prevent coagulation. With this method Stheeman found that many children showing anodal hyperirritability (Thie-

7. Stheeman, H. A.: Spasmophilia of Older Children, Jahrb. f. Kinderh. **36**:42, 1917.

mich's sign) have blood which is prevented from clotting by ninetieth or hundredth normal ammonium oxalate solutions. However, not all such children show this and some require even stronger than fiftieth normal solution to inhibit clotting. Thus, in a table of results, twelve so-called spasmophilics require only seventieth normal or weaker solutions; nine require sixtieth or fiftieth normal, and three require fortieth normal solutions to inhibit coagulation. In another table are given results of this method applied to diseases other than spasmophilia. One case of miliary tuberculosis did not clot with eightieth normal solution; two cases of rickets and "gastro-intestinal insufficiency" did not clot with seventieth normal solution. In this same table are reported thirteen cases of so-called spasmophilia requiring sixtieth normal or stronger solutions. They are, therefore, normal in this respect.

Stheeman now concludes that as one finds in these older children with Thiemich's sign the same low blood calcium as is found in infantile tetany, the two conditions are identical. He advocates the use of the terms "spasmophilic asthenia" or "asthenia of Erb's type" to designate the anodal hyperirritability in older children.

AUTHOR'S TESTS

The electrical excitability of 146 children, ranging in ages from 2 to 7 years were tested. The tests were performed in February and March, when spasmophilia is at its peak. The children were all inmates of an institution, had no ailments of any kind, were on a liberal diet and had the usual routine allowance of play, exercise in the open air and kindergarten attendance. The technic of the tests was described in the first paper of this series.

In Table 3 are given the average values found in the different age groups, together with the number and percentage of Chvostek's and of Thiemich's signs obtained.

TABLE 3.—AVERAGE VALUES OF ELECTRICAL EXCITABILITY AT DIFFERENT AGES

Age	Number Examined	C C C	A C C	A O C	C O C	A O C < A C C		Chvostek	
						Number	Per Cent.	Number	Per Cent.
2–3 years	27	1.9	4.1	4.3	>5	6	22	5	18
3–4 years	36	1.7	3.5	4.1	>5	8	22	12	33
4–5 years	53	1.9	3.6	4.3	>5	12	22	10	19
5–6 years	25	1.9	3.2	3.5	>5	10	40	9	36
6–7 years	5	1.6	3.8	3.4	>5	4	80	2	40
2–7 years	146	1.8	3.6	3.9	>5	40	27	38	26

In computing these averages one must remember that, as it is not desirable to try for a response with currents stronger than 5 ma., many of the values for the A C C and A O C, which may be very much greater than 5, are recorded only as "greater than 5" and are reckoned as 5 in the average. It is evident, therefore, that the above averages

for the A C C and A O C are lower than they should be. The number of children showing no response to currents of less than 5 ma. is shown in Table 4.

TABLE 4.—CHILDREN SHOWING NO RESPONSE TO CURRENTS OF LESS THAN 5 MILLIAMPERES

Age	No. Examined	A C C > 5		A O C > 5	
2–3 years	27	12	44%	18	66%
3–4 years	36	2	5%	21	60%
4–5 years	53	9	17%	33	62%
5–6 years	25	2	8%	11	44%
6–7 years	5	2	40%	1	20%

Table 3 shows that from the second to the fifth year Thiemich's sign occurs quite regularly in 22 per cent. of the children. Between the fifth and the sixth year, 40 per cent. had such anodal reactions, while the number of children over 6 years of age is so small that the high percentage of these reactions means little. It is significant, however, that Holmes found that 75 per cent. of children at this age gave the anodal reactions of Thiemich.

As might be expected, if any pathologic significance is to be attached to Thiemich's sign in older children, girls show these reactions more frequently than boys. Of sixty-three girls tested, twenty-one, or 33 per cent. were positive; nineteen of eighty-three boys, 23 per cent., reacted in this manner. It is interesting to note that between the second and fifth years more than 60 per cent. of the children have A O C > 5.

What is the relation between Chvostek's sign and Erb's phenomenon? Holmes found only one positive Chvostek in children under 5 years. I obtained it in twenty-seven. In testing for this sign, one must be careful to tap over the nerve with sufficient force. I have repeatedly obtained a definite Chvostek with a harder tap when I had almost put it down as negative because of failure to respond to a gentle tap. Of the forty children exhibiting Thiemich's sign, fourteen (35 per cent.) had positive Chvostek's (seven boys and seven girls), while the total number of Chvostek signs obtained was thirty-eight (twenty girls, or 31 per cent. and eighteen boys, 21 per cent.). I have not found that the older children show this sign more frequently than the younger, as Stheeman records, nor do I obtain lower electrical values in those children who have both Erb and Chvostek signs. On this point I am not in agreement with Stheeman.

With the exception of enuresis, no very definite information was obtainable about such symptoms as have been described by others as constituting spasmophilia, namely, petit mal, digestive disturbances, vasomotor instability. Practically all institutional children up to 3 years wet themselves. Among children more than 3 years old, wetting occurred as follows: Of fifty-one girls, twenty-two wet themselves,

and eight of these showed Thiemich's sign; of sixty-nine boys, 35 wet the bed or their clothes and eight of these exhibited Thiemich's sign. In none was a history of petit mal, breath holding spells or absences obtained. Some of the children had milder digestive upsets such as vomiting, diarrhea or constipation, but these seemed not to be related to their electrical irritability. Some were underweight, but time and again I was astonished to obtain so-called anodal hyperirritability in robust, well nourished children, exhibiting no fear of being tested and in no way neurotic or of the "cry-baby" type.

It was stated above that a study of this kind carried out in the summer months would be interesting by comparison with a study in the season when spasmophilia and tetany are at their height. A repetition of this work is now being planned for August.

SUMMARY

1. The work of Holmes and of Stheeman on the electrical reactions and their significance in older children is reviewed.

2. Electrical tests were performed on 146 healthy children between the ages of 2 and 7 years, living in a modern child-caring institution.

3. The average values found in these children are: C C C, 1.8; A C C, 3.6; A O C, 3.9; C O C, > 5.

4. Thiemich's sign occurred in forty instances, or 27 per cent.

5. Chvostek's sign was obtained in thirty-eight cases, fourteen of which, or 35 per cent., also manifested Thiemich's sign.

6. Enuresis occurred often, but only a small percentage of these children had Thiemich's sign.

7. Over 60 per cent. of 116 children between the ages of 2 and 5 years have an A O C > 5, while over 20 per cent. at these ages show A O C $<$ A C C and < 5.

8. The incidence of Thiemich's sign is somewhat higher in girls than in boys.

9. In no case was Escherich's sign (C O C < 5) obtained.

CONCLUSIONS

I heartily agree with those who state that it is difficult to interpret the electrical reactions of older children. In general, in view of the increasing frequency with which so-called anodal hyperexcitability reactions are obtained as the child grows older, it is safe to assume that those are the reactions one may expect to find and they should not, therefore, constitute a diagnosis of spasmophilia in the entire absence of all clinical symptoms.

Thiemich's sign in older children does not necessarily point to a neurotic or spasmophilic constitution.

The writer wishes to acknowledge his gratitude to Dr. Alfred F. Hess of New York for many privileges granted in carrying out this study.

EMPYEMA IN INFANTS AND YOUNG CHILDREN*

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In reviewing the literature on empyema in infants and young children, it was found that the number of extensive articles on this subject was surprisingly few. Since the majority of admissions to the Babies' Hospital are children under 3 years of age, an exceptional field is offered to observe this disease in the very young. For this reason it seemed worth while to make a study of the cases which have been treated during the last seven years. The cases treated prior to this time were analyzed in 1913 by Holt.[1]

From Jan. 1, 1913 to Jan. 1, 1920, 204 cases of clinical empyema were treated at the Babies' Hospital. Of this number 113 babies recovered and 91 died, a mortality of 44.6 per cent. Cases are classed as empyema in which pus or cloudy serum was obtained from the pleural cavity by exploratory punctures. From this pus or seropus bacteria were always grown. In six instances only a few cubic centimeters of cloudy serum were obtained, the infant recovering after puncture without the accumulation of more exudate in the pleural cavity. Cases of this type, from which bacteria were cultivated from the exudate, are included as examples of empyema.

INCIDENCE

The combined cases of pneumonia and empyema, which were admitted to the hospital during the period in which this series of cases was studied, numbered 1,869. Approximately, then, 11 per cent. of all the pneumonia patients either had an empyema at the time of admission or developed it in the hospital. This incidence of one empyema to nine pneumonias corresponds very closely to that of Dunlop,[2] who in a study of ninety-eight children with empyema found the frequency to be one empyema to every eight or nine pneumonias. Churchill,[3] on the contrary, states that this complication is relatively infrequent in children, empyema occurring once in every twenty cases of pneumonia.

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*From the records of the Babies' Hospital, New York.

1. Holt, L. E.: The Siphon Treatment of Empyema in Infants and Young Children Compared With Other Measures: A Study of 154 Cases, Am. Med. **8**:381 (June) 1913.

2. Dunlop, H. G. M.: Empyema in Children, Edinburgh M. J. **13**:1, 1914.

3. Churchill, F. S.: Empyema in Children with Special Reference to Diagnosis, Boston M. & S. J. **181**:87 (July 24) 1919.

The mortality by ages is given in Table 1.

TABLE 1.—AGE AND MORTALITY

Months	Total Cases	Recovered	Died	Mortality, per Cent.
0– 3	3	1	2	66.7
3– 6	17	4	13	76.5
6–12	33	14	19	57.6
12–24	85	42	43	50.6
26–36	37	27	10	27.0
Over 3 years	29	25	4	13.8

This table shows that the age of the infant is perhaps the largest single factor concerned in determining the prognosis. Among the twenty patients under 6 months of age, the mortality was 75 per cent.; among the fifty-three infants under 1 year, the mortality was 64 per cent., while for the twenty-nine over 3 years of age, the mortality was only 13.8 per cent.

The youngest case in this series was an infant only 22 days old. He was a male child admitted when fourteen days old with diarrhea of two days duration. The admission weight was 7 pounds. The physical examination revealed a definite pulmonary consolidation at the right base. Eight days after admission the physical signs at the right base were suggestive of fluid. An exploratory aspiration was done and pus was obtained. Continuous drainage by the syphon method was instituted under local anesthesia. The tube remained in the chest for sixteen days. Three days after its removal the baby was discharged in good condition. The temperature ranged between 99 F. and 103 F. before operation. It became normal the day after operation and remained so until discharge. Two blood cultures gave negative results. The white blood count was 44,000; polymorphonuclears 84 per cent., lymphocytes 16 per cent., the day after admission. The organism found was *Staphylococcus aureus* in pure culture. The baby was breast fed while in the hospital, and weighed 6½ pounds on the day of discharge. An observation four months afterward showed that he was thriving satisfactorily.

There were four cases of recovery in infants between 3 and 6 months of age. Pneumococcus was the organism found in the pus from the pleural cavity in three cases, staphylococcus in one. Siphon drainage was the treatment employed in three of these, and the tube remained in the chest nine, fifteen and sixteen days respectively. In the fourth case, an infant 5 months old, two aspirations were done and a total of 9 c.c. of seropus containing many pneumococci was obtained. This patient recovered without the removal of any more fluid from the pleural cavity.

SEX

There were 124 boys and 80 girls in this series. That the disease is so much more frequent in males than in females is rather surprising. The difference in this series is, however, not so marked as in the series of 154 cases reported by Holt,[1] in which 104 cases occurred in male infants and only 50 cases in females. The mortality for the males was 43.6 per cent., while that for the females was 46.3 per cent.

TABLE 2.—CONDITIONS ASSOCIATED WITH EMPYEMA

	Cases	Recovered	Died
Primary pneumonia	168	102	66
Pneumonia complicating measles	12	5	7
Pneumonia complicating whooping cough	4	2	2
Pneumonia complicating diphtheria	1	0	1
Pneumonia complicating varicella	1	0	1
Pneumonia complicating gastro-enteritis	9	3	6
Pneumonia complicating miliary tuberculosis	4	0	4
Pneumonia complicating retropharyngeal abscess	1	0	1
Pneumonia complicating tonsil and adenoid operation	2	1	1
Pneumonia complicating syphilis	2	0	2

Pneumonia was present in every case of this series. In 168 instances the pneumonia was primary and uncomplicated. Of these infants 102 recovered and 66 died, a mortality of 39 per cent. These cases are interesting when compared with those in which the pneumonia occurred as a complication of the common contagious diseases of childhood. In this group there were eighteen cases with eleven deaths, a mortality of 61 per cent. Contagious diseases are not admitted to the Babies' Hospital. This group is, therefore, very small. The high mortality is even more significant when the ages of these children are taken into consideration. The mortality for the twelve measles cases was 59 per cent. None of these children was under 1 year of age; eight of them were between 1 and 2 years old, and four were between 2 and 3 years old. The mortality for the children of this age in the entire series was 43 per cent.

DURATION OF SYMPTOMS BEFORE OPERATION

It is a general opinion that the duration of symptoms before operation is a matter of much importance in prognosis. The influence of the duration of the symptoms before the operation on the mortality of the 168 cases of empyema complicating primary pneumonia is shown in Table 3.

In three of these cases the duration of the respiratory symptoms was less than one week before operation. Such a rapid development of empyema to the point where operation is needed is not common. Details of these three cases are of considerable interest.

TABLE 3.—EMPYEMA FOLLOWING PRIMARY PNEUMONIA, DURATION OF SYMPTOMS AND RESULTS

Duration of Symptoms	Cases	Recovered	Died	Mortality, per Cent.
0–1 week	3	1	2	67
1–2 weeks	36	17	19	53
2–4 years	80	51	29	36
4–6 weeks	30	23	7	23
6 weeks and over	19	10	9	47

REPORT OF CASES

CASE 1.—A male infant, aged 16 months, was admitted because of cough and fever for two days. The physical examination was suggestive of fluid in the right pleural cavity. An aspiration was done on the day of admission and 300 c.c. of pus was removed. Six days later 300 c.c. of pus was removed by a second aspiration. Eight days after admission siphon drainage was employed. The temperature became normal the second day after operation and the patient recovered. A culture of the pus from the chest showed a pure growth of pneumococci.

CASE 2.—A male infant, 3 months old, was admitted because of irritability and fever for one day. The physical signs of the left chest suggested fluid. Pus was obtained by an exploratory puncture the day after admission, and siphon drainage was employed. The infant died thirteen days after operation. The blood culture was sterile. The pus from the pleural cavity contained streptococci. The necropsy showed acute bronchopneumonia with fibrinopurulent pleurisy over both lobes of the left lung.

CASE 3.—A male infant, 4 months old, was admitted with a history of diarrhea for four days. Physical signs were typical of fluid in right chest posteriorly. Pus was obtained by an exploratory puncture two days after admission, and siphon drainage was employed. The infant died two days after operation. The pus from the chest contained streptococci. Necropsy showed fibrinopurulent peritonitis, fibrinopurulent pericarditis and extensive bronchopneumonia with fibrinopurulent pleurisy over the whole right lung. Streptococci were found in the culture of all these exudates.

In view of the fact that bronchopneumonia was present in the lung of the affected side in both cases which came to necropsy, the conclusion seems warranted that in none of these cases was the empyema primary. Every case of empyema in this hospital which has come to necropsy, showed the empyema to be secondary to pneumonia.

It is interesting to note in Table 3 that in those cases in which the symptoms had lasted less than six weeks before operation the mortality decreased with the duration of symptoms. In nineteen cases in which the symptoms had lasted six weeks or more before operation there was a mortality of 47 per cent. This is high when compared to a mortality of 23 per cent. in the thirty cases in which symptoms had lasted from four to six weeks before operation.

The high mortality of the cases in which symptoms were of short duration before the operation is undoubtedly due chiefly to the greater intensity of the infection. The high mortality in the cases in which operation was done late may be due to complications which interfere

with expansion of the lung, chronic thickening of the pleura and pericardium, carnification of the lung, etc. The lowest mortality is seen in the middle group of cases. Early cases include those of greatest severity, and very late cases include the neglected ones.

LOCATION OF THE DISEASE

The left side of the chest was involved in 109 cases; the right in 91 cases; both sides were affected four times. These four cases of double empyema present some points of interest. Three of the cases were fatal. Two patients were treated by aspiration and one patient was treated by siphon drainage. In the patient who recovered the disease did not develop on the two sides simultaneously. Siphon drainage was the treatment employed, and the operations were twenty days apart.

PHYSICAL SIGNS

The most important physical signs of fluid in the pleural cavity of the young child are flatness on percussion, and displacement of the heart. It is a rule in the Babies' Hospital to do an exploratory puncture in every acute respiratory condition in which flatness to percussion is present. Of course, only by puncture can purulent and serous exudations be distinguished. Displacement of the heart is of great importance in diagnosis when present. But when the amount of pus present is small, and in a large number of the cases in young children the empyema is localized, the displacement is slight or absent altogether. This sign was absent in more than one third of the cases studied. Bronchial breathing is more often present than absent and while it is usually feeble and nasal in quality, it is very often indistinguishable from that which is heard over consolidation of the lung.

The type of infection has considerable influence on the mortality of this condition, as shown in Table 4.

TABLE 4.—BACTERIOLOGY AND MORTALITY

	Cases	Recovered	Died	Mortality, per Cent.
Pneumococcus alone	142	82	60	42
Staphylococcus alone	32	18	14	44
Streptococcus alone	20	9	11	55
Bacillus of Pfeiffer alone	2	1	1	50
Mixed Infections				
Streptococcus and pneumococcus	2	1	1	50
Pneumococcus and bacillus of Pfeiffer	5	1	4	80
Staphylococcus and bacillus of Pfeiffer	1	1	0	0

The pneumococcus was present in pure culture in 70 per cent. of the cases; and this group shows the lowest mortality in the series. The highest mortality, 62 per cent., was among the cases (eight)

of mixed infection. The streptococcus cases showed the highest mortality of the single infections. There were twenty of these and their mortality was 55 per cent.

Holt [1] found that the staphylococcus infections were more frequent in the very young infants. The age and the type of infection in this series are given in Table 5.

TABLE 5.—AGE AND TYPE OF INFECTION

	First Year		Second Year		Third Year		Over Three Years	
	Cases	Died	Cases	Died	Cases	Died	Cases	Died
Pneumococcus.....	31	20	61	32	25	7	25	1
Staphylococcus.....	10	5	17	8	4	1	1	0
Streptococcus.....	9	7	3	1	6	1	2	2
Bacillus of Pfeiffer.	1	0	..	..	1	1		
Mixed infections....	2	2	4	2	1	0	1	1

This series of cases also shows a greater frequency of staphylococcus infections in the first and second years. Streptococcus infections are also more frequent during the first two years of life. Tubercle bacilli were not found in the pus in any instance, but general miliary tuberculosis was found at necropsy in four cases; the empyema, however, was non-tuberculous.

BLOOD EXAMINATION

A leukocyte count, together with the differential count, was made before operation in all but five cases.

The average count in cases ending in recovery was:

82 pneumococcus cases	31,900
18 staphylococcus cases	32,800
9 streptococcus cases	30,500
3 mixed infection cases	45,000

The average count in the fatal cases was:

58 pneumococcus cases	31,700
12 staphylococcus cases	37,500
10 streptococcus cases	44,000
5 mixed infection cases	23,000

Two cases with unusually low leukocyte counts are especially interesting. Both terminated fatally. One, a child of 3 years, had a leukocyte count of 7,200. The organisms present in the pus from the chest were pneumococcus and Bacillus of Pfeiffer. The case was complicated by a pneumococcus septicemia, pneumococcus pericarditis and miliary tuberculosis. In the other case, a child of 10 months, the leukocyte count was 9,800. A pure culture of pneumococci was grown from the pus obtained from the pleural cavity. Otitis media and ulcerative colitis were complications. The highest leukocyte count in the series was 83,000. This was seen in an infant 1 year old, who

died the day after operation. Pneumococcus was present in the pus from the chest. This case was complicated by a pneumococcus septicemia with pneumococcus meningitis.

It is evident that no conclusion as to prognosis can be drawn from the leukocyte count. The leukocyte count is also of little value in making the diagnosis between empyema and pneumonia. In many instances the empyema developed in patients under observation without any noticeable increase in the leukocytosis.

Blood cultures were made in 115 of the cases studied, of which 43 were positive and 72 were negative. This type of infection, and the mortality are shown in Table 6.

TABLE 6.—Prognostic Value of Blood Cultures

	Negative Cases	Died	Positive Cases	Died
Pneumococcus alone	51	18	34	20
Streptococcus alone	9	6	2	2
Staphylococcus alone	10	4	4	3
Bacillus of Pfeiffer alone	1	0	1	1
Mixed infections	1	1	2	2

It is to be noted that fifteen of the infants with general blood infection recovered. The blood culture of fourteen of these showed pneumococci; of one, staphylococci. The majority of these blood infections were found in cases in which there was a rapid general infection, and in which the empyema developed as a complication in the earlier stages of the pneumonia.

TABLE 7.—Results With Different Methods of Treatment

Type of Treatment	Cases	Recovered	Died	Mortality, per Cent.
Siphon drainage	142	86	56	39.4
Simple incision and drainage	29	14	15	51.7
Rib resection	9	5	4	44.4
Aspiration	24	8	16	66.6

The majority of these cases, it will be seen, were treated by siphon drainage. This method of treatment has been described by Holt.[1] Simple incision between the ribs and the introduction of one or two short rubber tubes was the treatment employed in twenty-nine cases. Rib resection was the primary operation in only nine of these children. In twenty-four the only treatment was aspiration; the number of aspirations done on a single patient varied from one to six. Aspiration was the method of treatment used only in those infants who were so acutely ill that it seemed unwise to do a more serious operation. The mortality, 66.6 per cent., in this group is for

this reason very high. In two of these cases (ages 7 and 13 months, respectively) 300 c.c. of pus were removed from the pleural cavity by three and four aspirations, respectively. Both these children recovered without other surgical interference. Pneumococcus was present in the pus from the chest of the younger, streptococcus in that from the chest of the older infant.

Dr. Homer F. Swift[4] in a study of pneumococcus empyema in adults, advises early operation as soon as the diagnosis has been made. In his experience all cases in which a pleural exudate containing bacteria was obtained, ultimately came to operation. This has not been the experience with infants and young children at the Babies' Hospital. In six cases a seropurulent exudate varying in amounts from a few drops to 15 c.c., and containing many pneumococci, was obtained by aspiration of the pleural cavity. These six patients recovered without any further removal of fluid.

TABLE 8.—AGE AND RESULTS BY DIFFERENT METHODS OF TREATMENT

Age	Siphon Drainage		Simple Incision with Drainage		Aspiration		Rib Resection	
	Cases	Died	Cases	Died	Cases	Died	Cases	Died
First year	36	20	8	7	9	7		
Second year	50	27	9	4	12	8	5	4
Third year	31	9	3	1	2	0	1	0
Over 3 years	16	0	9	3	1	1	3	0

It is to be noted in Table 8 that rib resection was not done on any infant under 1 year old. Yet the mortality for the nine children so treated is 44 per cent. Among those cases treated by siphon drainage and those by simple incision with drainage, the method chosen was not determined by the age; neither were certain types of cases, as mild or severe, chosen for the different methods of treatment.

The mortality of 39.4 per cent. in cases treated by syphon drainage is the lowest in the series. The best results with syphon drainage were obtained when this could be maintained without interruption as long as a week. The average number of days in which syphon drainage was maintained for the 86 cases who were treated by this method, and who recovered, was 6.4 days. In only fourteen of the fatal cases so treated was siphon drainage maintained six days or longer; and in all of these the fatal outcome was greatly influenced by complications. Siphon drainage has to be discontinued occasionally for one of two reasons: First, plugging of tube by masses of fibrin; second, air leakage around the tube due to faulty technic during operation or to ulceration around the tube.

4. Swift, H. F.: The Treatment of Empyema Caused by Pneumococci. Read before the New York Academy of Medicine, March 16, 1920.

One of the greatest difficulties in the way of the recovery of young infants with empyema is imperfect pulmonary expansion due to the soft thoracic wall and to feeble respiratory muscles. Treatment by siphon drainage favors early and easy expansion. Cotton [5] believes that the proper utilization of the knowledge of pneumodynamics in the treatment of empyema in children will lower the mortality, decrease the number of chronic cases, and furnish adequate means of treating chronic cases without frequent resort to the radical and deforming operations of the past. The superiority of siphon drainage over any other method of treatment of empyema in early infancy used in this hospital has been clearly demonstrated, and the observations of Cotton seem justifiable. The observations of Kelly,[6] on the other hand, are hardly warranted when he says that "pumps, siphons, valves and suction apparatus are more bother than they are worth in children."

COMPLICATIONS

Table 9 shows how frequent complications are with empyema, and that death is often due to causes not connected with the pulmonary condition.

TABLE 9.—Complications

	Recovered	Died
Otitis media	33	24
Pneumonia in opposite lung	4	22
Gastro-enteritis	12	25
Diphtheria	1	6
Erysipelas	1	3
Acute nephritis	1	2
Bacillary dysentery	1	
Miliary tuberculosis	..	4
Ulcerative colitis	..	2
Congenital heart disease	..	1
Peritonitis	..	3
Retropharyngeal abscess	..	1
Congenital syphilis	..	2
Osteomyelitis of rib	..	1
Measles	..	1
Meningitis (pneumococcus)	..	2
Meningitis (streptococcus	..	1
Meningitis (tuberculosis)	..	1
Pyelitis	..	4
No complications	40	4

Of the infants who died, four had definite miliary tuberculosis, three had peritonitis (the organism in each case was the same as that present in the pus from the chest), two, age 3 months each, had congenital syphilis, and four had meningitis. The complications in thirteen of these infants, therefore, were of such severity that there

5. Cotton, F. J.: Pneumodynamics of Empyema, Boston M. & S. J. **173**:800, 1915.

6. Kelley, S. W.: Drainage of Acute Pleural Empyema in Children, Am. J. Surg. **26**:47, 1912.

was little hope for their recovery whatever the treatment employed. The most interesting observation in Table 9 is the fact that among the fatal cases there were only four who did not present some serious lesion besides the pulmonary condition.

POSTMORTEM OBSERVATIONS

Necropsies were performed in sixty-four of the ninety-one fatal cases. These cases, grouped according to the anatomic diagnosis, are shown in Table 10. Lobar pneumonia was found in only three, while bronchopneumonia was present in fifty-five. This, of course, is due to the fact that bronchopneumonia is much more frequent during the first two years of life. It is interesting to note that Dunlop[2] states that empyema followed lobar pneumonia in 69 per cent of a series of ninety-eight cases studied by him. His series includes a much larger number of older children than does this series of cases.

TABLE 10.—NECROPSY FINDINGS IN SIXTY-FOUR FATAL CASES

	Cases
Bronchopneumonia	55
Lobar pneumonia	3
Carnification of the lung	10
Multiple pulmonary abscesses	8
Pseudomembranous pleurisy (Klebs-Loeffler origin)	1
Diphtheritic laryngitis	2
External pericarditis	20
Internal pericarditis	2
Miliary tuberculosis	4
Purulent peritonitis	8
Acute colitis	7
Purulent arthritis	1

Practically all cases coming to necropsy showed a fibrinopurulent pleurisy varying from a small amount of thin fibrin shreds to an extensive fibrinopurulent exudate, from 1 to 2 mm. in thickness; the lesion was double in nine cases. External pericarditis was found in twenty cases. This was more frequently found in those cases in which the left side was involved. Purulent peritonitis was present in eight cases; in five, this condition had not been recognized during life.

There was only one case of empyema necessitatis, or external opening through the thoracic wall in this series; and in no instance was there a rupture of the pus into a large bronchus or into the esophagus; nor did the pus burrow behind the diaphragm, causing a psoas or subdiaphragmatic abscess. Localized empyema was frequent. The pus cavity was localized in the majority of cases which came to necropsy; but in no instance was interlobar empyema seen either at necropsy or at operation.

DURATION OF LIFE AFTER OPERATION IN FATAL CASES

Of the fatal cases treated by siphon drainage, twenty-three patients died within the first week, while twenty lived twelve days or longer after operation. All of the patients on whom rib resection was done lived longer than twelve days; and five of the cases treated by simple incision with drainage lived twelve days or longer. In nearly one third of these cases, then, the death was probably from exhaustion due to prolonged sepsis and to imperfect expansion of the affected lung. These patients died in spite of the fact that in every instance the drainage was perfect.

TIME OF OPERATION

It is the experience of the Babies' Hospital, unless the accumulation of fluid in the pleural cavity is very rapid, that the infant's chances of recovery are improved by delaying the operation until the acute inflammatory process in the lung itself has subsided. In some of these cases aspiration may be done for temporary relief, the opening of the chest being deferred.

CONCLUSIONS

1. The mortality of empyema in infants and very young children is high with all methods of treatment employed.

2. Approximately 11 per cent. of all the cases of pneumonia admitted to the Babies' Hospital during the last seven years either had empyema at the time of admission or developed it during the stay in the hospital.

3. The mortality in empyema decreases very rapidly as the age of the infant advances.

4. Empyema was the sequel of pneumonia in every case of this series. When pneumonia is a complication of the common infectious diseases of childhood the mortality is very high.

5. Pneumococcus in pure culture was present in the pus from the pleural cavity in 70 per cent. of these cases; the mortality for this type of infection is the lowest in the series.

6. The degree of leukocytosis is no guide to prognosis or to diagnosis.

7. In the experience of the Babies' Hospital siphon drainage has given better results in the treatment of empyema in infancy than any other method of treatment employed.

The writer wishes to express thanks to Dr. L. Emmett Holt for permission to use the hospital records in making this report and for his assistance in its preparation.

A STUDY OF THE URINE SUGAR IN INFANTS*

ROY M. GREENTHAL, M.D.

NEW YORK

It has long been considered probable that the urine of normal individuals contains a reducing sugar. Benedict, Osterberg and Neuwirth [1] recently demonstrated the constant presence of sugar in normal urine and devised a method for its quantitative determination. They found that the amount of sugar in the urine was directly influenced by the quantity of sugar ingested. They also demonstrated that the urine sugar can be separated into two fractions by fermentation with yeast, a fermentable and a non-fermentable portion.[2]

During the course of work in this laboratory on the sugar tolerance of infants, a number of determinations of urine sugar have been made. These determinations have led to observations which seem of sufficient interest to report.

Technic.—The infants on whom observations were conducted were all practically normal in the sense of being free from infections or gastro-enteric disturbances. Many were of normal weight, a few were underweight for their age. All of the patients were under 7 months of age. If at any time an infant became ill, observations were discontinued until after complete recovery. Most of the infants were on four hour feeding intervals and received six feedings daily. The urine was usually collected over a period of eight hours. Each separate voiding was immmediately transferred to a bottle kept on ice and as a further precaution toluene was added as a preservative. The analyses of the urines were made as soon after collection as possible. These precautions are necessary, as much of the sugar present in the urine is very easily lost by fermentation when kept in a warm room. The determinations were made according to the method of Benedict and Osterberg with a few slight modifications. In order to insure complete precipitation of all reducing substances other than sugar, urines with a specific gravity of more than 1.010 were diluted with sufficient water to reduce the specific gravity to that point. The mercuric

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* From the Children's Service at the New York Nursery and Child's Hospital (Dr. Oscar M. Schloss, Director), and the Department of Pediatrics, Cornell University Medical College.

1. Benedict and Osterberg: J. Biol. Chem. **24**:195, 1918. Benedict, Osterberg and Neuwirth: J. Biol. Chem. **24**:217, 1918.

2. Throughout this report, the reducing substance in urine which is not fermented by yeast will be referred to as non-fermentable sugar. The exact nature of this substance is unknown at present.

nitrate reagent was diluted with water in the proportion of seven parts of the reagent to three parts of water. In producing the color reaction, the tubes were immersed in boiling water for twenty minutes [3] instead of ten minutes.

In all specimens the total sugar was determined and also the non-fermentable portion was determined by fermenting the urine with yeast for from 18 to 24 hours. The fermentable portion was derived by subtraction.

The twenty-four hour sugar excretion was calculated on the basis of the period of observation. Each specimen of urine was tested with Benedict's qualitative reagent.

At the beginning of the observations, the baby was usually placed on a formula consisting of 1½ ounces of milk per pound of body weight in order to fulfil the fat and protein requirements. Sugar was added in moderate amount and then gradually increased at from three to four day intervals, leaving the rest of the formula constant. In this way the relation of the amount of sugar secreted in the urine to the amount of sugar ingested was studied. In some cases the sugar was first increased and then reduced in order to ascertain further the relation of the sugar in the food to the urine sugar. Frequent analyses of the urine sugar were made on other infants whose formula was unchanged. This was to determine the sugar excretion, both fermentable and non-fermentable on the basis of a constant sugar intake.

AMOUNT OF SUGAR IN INFANT'S URINE

One hundred and seventy urine sugar determinations were made on 37 infants. Considering all cases, the calculated twenty-four hour total sugar excretion varied from 100 to 815 mg. The non-fermentable portion varied from 45 to 253 mg. Similar to the work of Benedict, Osterberg and Neuwirth on adults, our results show that the amount of urine sugar in infants is dependent to a considerable degree on the amount of sugar ingested. For this reason, the larger values obtained by us do not indicate the normal sugar excretion, as in many cases the infants received much larger amounts of sugar than are usually fed. Considering only the amount of urine sugar in infants receiving from 6 to 7.5 per cent. sugar, the values for total sugar range from 100 to 400 mg., and for the non-fermentable portion from 45 to 150 mg. Benedict, Osterberg and Neuwirth found that adults excrete from 600 to 1,200 mg. of total sugar on an ordinary diet. The non-

3. These modifications were made at the suggestion of Dr. Benedict (personal communication to Dr. Schloss).

fermentable portion varied from 340 to 660 mg. As would be expected, infants excrete a smaller absolute amount of sugar, but the amount in proportion to body weight is much greater.

It was found that the quantity of sugar excreted is quite independent of the volume of urine. For example, one infant, A. H., excreted 65 c.c. of urine containing 63 mg. of sugar during one period. At another time he excreted only 28 c.c. of urine during a period of equal length, but this specimen contained 76 mg. of sugar. The first urine contained 97 mg. of sugar per hundred c.c., while the second contained 228 mg. per hundred c.c.

TABLE 1.—SHOWING EFFECT ON URINE SUGAR OF FEEDING INCREASING AMOUNTS OF SUGAR. A. G., AGED 4 MONTHS. COLLECTION PERIOD 8 HOURS: 8 A. M. TO 4 P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable, Sugar, Mg.	Weight, Pounds and Ounces		Formula	Benedict's Qualitative Test
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar		Lb.	Oz.		
2/ 5	95	0.056	52.9	0.031	29.5	57	23.4	11	5	Milk, 20 oz. Lactose, 1 oz. Barley water to 30 oz. 6 × 5 oz.	0
2/16	125	0.047	58.6	0.017	21.8	38	26.8	11	11	Milk, 22 oz. Lactose, 1½ oz. Barley water to 30 oz. 6 × 5 oz.	0
2/28	70	0.167	116.6	0.040	27.2	24	93.2	12	4	Milk, 22 oz. Lactose, 2½ oz. Barley water to 30 oz. 6 × 5 oz.	+
3/ 5	80	0.158	130.1	0.035	28.4	22	101.7	12	8	Milk, 22 oz. Lactose, 3½ oz. Barley water to 30 oz. 6 × 5 oz.	+
3/10	75	0.186	139.8	0.039	29.4	20	110.4	13	4	Milk, 22 oz. Lactose, 4 oz. Barley water to 30 oz. 6 × 5 oz.	+

Relation of Sugar Intake to Sugar in Urine.—It has been mentioned that the excretion of sugar in the urine is directly dependent on the amount of sugar ingested. This was found to be true of all the cases studied. An example of a typical case is given in Table 1. It will be seen that as the sugar in the formula was increased, the total urine sugar was also increased. The increased excretion of sugar was confined chiefly to the fermentable portion. It is also to be noted that as the total urine sugar increased the percentage of nonfermentable sugar became less. On the first formula the nonfermentable sugar was 57 per cent. of the total and on the last formula, which contained

the greatest amount of sugar, the nonfermentable portion dropped to 20 per cent. of the total. The total urine sugar excreted on the last formula was nearly three times as great as on the first formula.

TABLE 2.—Showing Sugar Excretion in Urine When Sugar Was First Increased and Then Decreased. R. H., Aged 5 Weeks. Collection Period 8 Hours: 8 A. M. to 4. P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable, Sugar, Mg.	Weight, Pounds and Ounces		Formula	Benedict's Qualitative Test
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Total Sugar		Lb.	Oz.		
4/ 9	68	0.099	59.6	0.031	21.6	36	38.0	9	4	Milk, 13 oz. Dextri-maltose, 1 oz. Barley water to 24 oz. 6 × 4 oz.	+
4/16	57	0.136	75.7	0.047	26.8	35	48.9	9		Milk, 14 oz. Dextri-maltose, 1½ oz. Barley water to 24 oz. 6 × 4 oz.	+
4/21	55	0.213	116.9	0.064	35.0	30	81.9	9	8	Milk, 14 oz. Dextri-maltose, 2 oz. Barley water to 24 oz. 6 × 4 oz.	+
4/29	53	0.251	132.6	0.059	31.5	23	101.1	9	10	Milk, 14 oz. Dextri-maltose, 2½ oz. Barley water to 24 oz. 6 × 4 oz.	+
5/11	27	0.179	48.3	0.085	22.9	47	25.4	8	15	Milk, 12 oz. Dextri-maltose, 1 oz. Barley water to 24 oz. 6 × 4 oz.	+
5/17	81	0.106	86.1	0.042	33.9	40	52.2	8	14	Milk, 12 oz. Dextri-maltose, 1½ oz. Barley water to 24 oz. 6 × 4 oz.	+

In Table 2 are given the results of increasing the ingested sugar and then decreasing it. The rise and fall of the sugar excretion in the urine is clearly shown. The loss of weight between April 29 and May 11 was due to an intercurrent infection (rhinopharyngitis) during which time the patient was on a low formula and no determinations were made. The determination on May 11 was made one week after recovery as the sugar was being gradually increased again. It will also be noted that on two occasions during the observations (April 16 and May 17) the formula was practically the same. The sugar excretion, total, fermentable and nonfermentable, was practically constant. The collection periods were both of eight hours' duration but the amount of urine excreted was nearly 50 per cent. greater on May 17 than on April 16. This shows again that the amount of sugar in the urine is quite independent of the volume of urine.

In Table 3 the sugar excretion on a given formula is shown. It will be seen that the amount of sugar excreted remained practically constant. In adults this was also found to be true by Benedict, Osterberg and Neuwirth.

In this series of 170 determinations, a positive reaction with Benedict's qualitative sugar reagent was obtained in seventy-one. As a rule, the test was positive when the urine contained approximately 0.1 per cent. or more of sugar.

TABLE 3.—SHOWING URINE SUGAR EXCRETION WITH CONSTANT SUGAR INTAKE. C. N., AGED 2 MONTHS. FORMULA: MILK, 12 OUNCES; DEXTRI-MALTOSE, 1¾ OUNCES; BARLEY WATER TO 24½ OUNCES; 7 × 3½ OUNCES. COLLECTION PERIOD 6 HOURS: 8 A. M. TO 2 P. M.

Date	Urine, C.c.	Total Urine Sugar		Nonfermentable Sugar			Fermentable Sugar, Mg.	Weight	
		Per Cent.	Mg.	Per Cent.	Mg.	Per Cent. of Tatal Sugar		Lb.	Oz.
11/29	55	0.092	50.8	0.037	19.3	38	31.5	8	5
12/ 2	80	0.068	54.6	0.032	25.8	47	28.8	8	6
12/ 5	80	0.055	44.0	0.023	18.0	41	26.0	8	8
12/ 8	130	0.045	58.2	0.022	29.0	49	29.0	8	8

Our results lead to conclusions quite opposed to those of Porter and Dunn.[4] They examined the urines of infants who received large amounts of sugar in their food and concluded that there was no direct relationship between the amount of sugar ingested and the presence of sugar in the urine. The difference between their results and ours is probably due in part to the fact that they used a purely qualitative test for sugar and did not estimate the total sugar output. A qualitative test is positive only when the urine contains sugar in a definite concentration and is in no way indicative of the actual sugar output.

For example, 100 c.c. of urine containing 0.1 gm. of sugar would probably give a positive reaction with a copper reduction test, while 0.15 gm. of sugar in 200 c.c. of urine, which represents a larger output of sugar, would probably not reduce a copper test solution owing to the lower sugar concentration. F. H., receiving a moderate amount of sugar, excreted 40 c.c. of urine in eight hours containing 53 mg. sugar. The urine contained 0.33 gm. of sugar per 100 c.c., and Benedict's qualitative reagent was reduced. J. T., receiving a large amount of sugar, excreted 255 c.c. of urine in eight hours containing 147 mg. sugar. The sugar concentration of this urine was only 0.058 gm. per hundred c.c., and Benedict's test was negative.

4. Porter and Dunn: Am. J. Dis. Child. **10**:77 (July) 1915. Dunn: Pediatrics, Ed. 1 **2**:475.

Porter and Dunn make no mention of what length of time elapsed between the collection and examination of the urine specimens. It has been our experience that the amount of sugar will diminish very rapidly unless the specimen is very carefully preserved.

As mentioned previously, based on a quantitative determination of the urine sugar, our results show definitely that with increased ingestion of sugar there is an increased elimination of sugar in the urine. Based on a qualitative test alone, the greater number of positive reactions occurred when large amounts of sugar were given but positive reactions also occurred when moderate or small amounts of sugar were fed. In such instances, the urine was concentrated.

On the basis of these results, it seems that the quantitative determination of the urine sugar may prove of distinct value in estimating sugar tolerance. Its use in this connection will be the subject of a separate report.

CONCLUSIONS

1. The urine of all normal infants contains a determinable amount of reducing sugar.

2. The amount of sugar excreted is not dependent on the volume of urine but is directly proportional to the amount of sugar ingested. As the amount of sugar in the diet is increased, the total urine sugar increases. This increase is chiefly in the fermentable portion and as a result the percentage of nonfermentable sugar becomes less.

3. Sugar excretion in infants, both fermentable and nonfermentable, is fairly constant when the intake of sugar is constant.

I desire to express my appreciation to Dr. Oscar M. Schloss, at whose suggestion the problem was undertaken, for his kind criticism and advice during this study. I also desire to acknowledge my indebtedness to Miss Elizabeth S. Morris, nurse in charge of the children's wards, for invaluable aid in supervising the patients on whom observations were conducted.

BOOK REVIEW

PROPHYLAXIS AND THERAPY OF CHILDREN'S DISEASES. By Prof. F. Göppert (Göttingen) and Prof. L. Langstein (Berlin). Cloth. Price, 42 marks (plus). Pp. 606, with 37 illustrations. Berlin: Julius Springer, 1920.

This is a new textbook on children's diseases by two of Germany's foremost pediatricians. Infant feeding and infant care in health and disease receive careful attention. As the volume is intended for the practitioner, therapy receives much attention. The chapter on "medicinal therapy" is rather extensive, including prescriptions containing rather obsolete vegetable derivatives as well as rather extensive lists of modern German pharmaceuticals; e. g., under urinary antiseptics there are included: cystopurin, hippol, myramalid, amphotropin, etc. The authors claim to have seen no benefit from tonsillectomy in cases of chronic arthritis nor do they think that bathing eczema cases with water a few times a week acts harmfully. Their antisyphilitic treatment is very good. The paucity of illustrations is the shortcoming of the volume. The one showing longitudinal sinus puncture for obtaining blood and that of injection into the temporal vein are good.

CORRECTION

In the paper by Milo K. Miller and Karl M. Nelson, "Elephantiasis Congenita Angiomatosa (Unna), Associated with Changes in the Capillaries," published in the American Journal of Diseases of Children, August, 1920, p. 127, an erroneous legend was attached to Figure 3: "The degree of development of lymph vessels and blood vessels in early months of life." As stated in the text, this figure is taken from the paper by Holland and Meyer, *München. med. Wchnschr.*, **66**:1191, 1919. The manuscript did not contain this legend, and this figure represents capillaries.

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